SG-HSA eCTD Specification and Guidance for Use

Module 1 and Regional Information

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1. Introduction

This document applies to all Applications for all types of therapeutic product Submissions using the electronic Common Technical Document (eCTD) format in Singapore.

It is important to understand that the CTD structure is flexible and can be as detailed or as simple as the type of Submission requires. In some cases, content should be provided in most of the sections defined in Modules 1-5. In other cases, very little content will be required in Modules 4 and 5. Guidance on what content should be provided for the different Submission Types is provided in the Document Matrix and Guidance on Therapeutic Products Registration in Singapore.

This eCTD Specification version is based on the ICH eCTD version 3.2.2 Specification.

This document contains:

- guidance on the structure of a Singapore eCTD Application; and
- guidance on creating and validating your Singapore eCTD Sequences.

The HSA eCTD Specification should be read in combination with:

- Guidance on Therapeutic Products Registration in Singapore
- Guidance on Change of Registrant for Registered Therapeutic Product
- SG-HSA eCTD Validation Criteria
- SG-HSA eCTD Q&A Document

The eCTD Specification is designed to assist software vendors and technical staff with understanding of the technical setup and creation of a Singapore eCTD. We encourage regulatory personnel to read and understand the Specification at a high level and focus on the information provided in 2. Preparing your Singapore eCTD Application and 3. Singapore Regional Considerations, the Guidance on Therapeutic Products Registration in Singapore, sections 2, 4 and 6 of the SG-HSA eCTD Validation Criteria and information clarified in the SG-HSA eCTD Q&A Document.

Comment about ICH eCTD version 4.0

Internationally, the eCTD is currently implemented using the ICH eCTD version 3.2.2 Specification. The eCTD Specification for version 4.0 has been released and some agencies are in the process of implementing plans to migrate. It is the intention of Singapore to also migrate once experience has been obtained by other authorities and a smooth transition can be planned.

1.1. Terminology

It is acknowledged that the terminology to describe electronic Applications differs between regions. In addition, there is an effort to harmonise terminology in anticipation of a future migration to eCTD version 4.0. Hence, the terminology in the SG-HSA Specification is mostly consistent with the proposed terminology in the ICH eCTD version 4.0 Specification. To assist users interpreting this Specification, a brief list of terms used in this document is described below:

Table 1 eCTD Terminology

Term	Definition
Applicant	The company responsible for the eCTD Application.
Application	A collection of electronic documents provided over a period of time. The Application refers to the entire life cycle of registration(s) filed under a HSA SG eCTD ID. An Application is comprised of all Submissions and Sequences over time. *Application is a term consistent with the eCTD version 4.0 Specification but was often referred to as a Submission or Dossier in earlier versions.* *Application as used in PRISM is mostly equivalent to the eCTD Submission.*
Authority	Refers to the entity responsible for the evaluation and/or approval of applications for a particular region. In Singapore, this refers to the Health Sciences Authority (HSA).
Baseline	A Sequence providing information already submitted to and approved by HSA in a non-eCTD format.
CTD	Common Technical Document as defined by ICH and HSA. Modules 2-5 are based on the ICH internationally accepted structure for Quality, Nonclinical and Clinical Information. Module 1 and sections 2.3.R / 3.2.R Regional Information are defined by HSA.
eCTD	Electronic Common Technical Document – an international electronic standard for the Common Technical Document (CTD) providing the means for transferring information from pharmaceutical companies to Authorities.
Elements	XML Elements are defined structural components of the eCTD. The Elements structure the content and data so that the Application can be managed and displayed over the entire life cycle of the product.
Envelope	Envelope contains the metadata relevant to the eCTD Sequence. Metadata are referred to as Envelope Elements. ICH and some regions refer to the Envelope as the Administrative Information.
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
Leaf	Structural element of an eCTD Submission delivering a document. It provides the information about the file provided including a unique ID and checksum, saved location, and life cycle operation along with the title associated with the linked content. Leaf titles are crucial for efficient evaluation of eCTDs. Evaluators will see the Leaf titles and NOT file names which are irrelevant for eCTD applications.
OCR	Optical Character Recognition. Process by which software recognises text within a digital image e.g., scanned document. OCR software converts images into readable text that can be searched and copied.
RTF	Rich Text Format is a word processing or operating system independent format.
SG eCTD ID	A unique identifier generated by HSA eCTD Portal that is associated to a company (Entity ID) for an eCTD Application.
Submission	A collection of Sequences covering a specific request which includes the first Sequence of the activity and any follow-up Sequences e.g., supplemental information, response to recommendations, withdrawals, etc.

	Submission is a term consistent with the eCTD version 4.0 Specifications but was often referred to as a Regulatory Activity in earlier versions. *Submission is often referred to as Application in PRISM.*
Sequence	A Sequence is a package of information bundled together in an electronic structure providing information to the agency. The contents of a Sequence depend on the Submission Type and whether it is the initial Sequence of the Submission or a follow-up providing additional data or changes.

Application vs. Submission vs. Sequence Diagram

It is important to understand the relationship between the different levels of an ongoing application as applied to life cycle management.

- The Application level is the highest overall level representing the product. It can contain multiple strengths of the same product and multiple pharmaceutical forms. An Application is made up of multiple Submissions.
- The Submission level represents regulatory activities which may each be made up of one or more Sequences. The Sequences assigned to a Submission may not be sequential as parallel Submissions may be under review causing some Sequences to be skipped within a Submission. Each time a new activity is started, a new Submission will be created.
- The Sequence level is the lowest level representing each package of information provided. Each Sequence must be assigned to a Submission either as the initial Sequence or as a follow-up Sequence in the form of supplemental information, a response, withdrawal or closing information.

Note that the eCTD construction allows the evaluator via the evaluation system to filter and adjust their view to focus on the content included in a Sequence, Submission, or current Application as a whole or to show only content provided in approved Submissions.

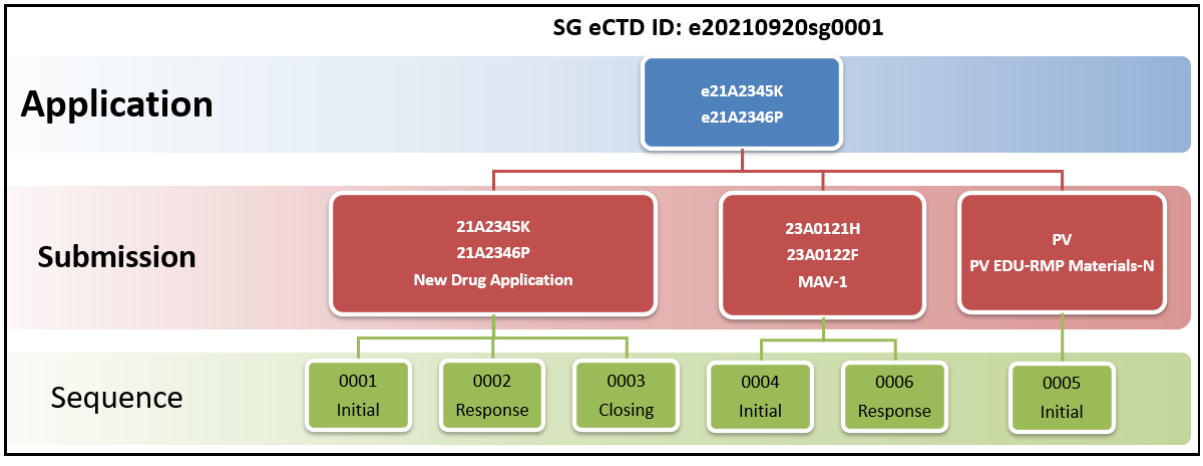

Figure 1 Application, Submission and Sequence Relationship

2. Preparing your Singapore eCTD Application

2.1. The Company (Entity ID)

The company's Corppass[1] Entity ID is required and is used to identify the Applicant.

The Entity ID should be used for all future applications even if the company name changes.

2.2. The SG eCTD ID

The SG eCTD ID is a unique number issued via the HSA eCTD Portal upon request by an Applicant. This SG eCTD ID is associated with the company (Entity ID) and cannot be deleted or amended once issued. The SG eCTD ID is required for submission of any eCTD package to HSA via the HSA eCTD Portal.

Once used for a specific eCTD Application, the SG eCTD ID remains associated with that Application for the rest of the product life cycle. The SG eCTD ID also remains unchanged regardless of additions and withdrawals of products contained in the Application. The SG eCTD ID is to be used as the Application Folder Name in all eCTD submissions for a specific Application (see 2.8 eCTD Application Folder Naming Convention).

Example: e20220920sg0001

2.3. The Application Number

Each product in an Application should have a unique Application Number. A prefix of "e" should be added to the Application Number for all eCTD applications. The prefix is followed by the application number issued for the NDA or GDA in PRISM (case-sensitive) or the Drug Master File (DMF) number to form the eCTD Application Number.

If multiple strengths are combined in a single eCTD Application, then the Application Number of each strength should be listed in the eCTD Application.

Example: PRISM application number = 2212345A, eCTD Application Number = e2212345A

Example: PRISM application numbers (GDA-1 + GDA-2) = 21A3456P, 21A5678K, eCTD Application Numbers = e21A3456P, e21A5678K

Example: DMF number = 015:688, eCTD Application Number = e015:688

The Application Number is valid throughout the entire life cycle of a product and is connected to the product, not a specific Applicant. When products are transferred to other Applicants, the Application Number does not change.

[1] Corppass is the authorisation system for entities to manage digital service access of employees who need to perform corporate transactions.

2.4. The Submission Number

The application number provided by PRISM serves as the Submission Number for all NDA, GDA, MAV, MIV and transfer submissions.

Please enter “DMF” as the Submission Number for all DMF submissions, including baseline and transfer situations.

Please enter “PV” as the Submission Number for all pharmacovigilance (PV) submissions.

Please enter “Other” as the Submission Number for other regulatory activities.

All Submission Numbers used in eCTD are case-sensitive and should be entered as shown in Table 2.

Table 2 eCTD Submission Number Definitions

Type of eCTD Submission	eCTD Submission Number (case-sensitive)
NDA GDA MAV MIV Transfer of eCTD Application	PRISM application number(s)
Pharmacovigilance submissions	“PV”
All DMF related submissions (i.e., product type is DMF)	“DMF”
Submission to fulfil registration condition Baseline submission Other regulatory activities	“Other”

Each new Submission in eCTD requires a new Submission Number. The Application Number remains unchanged from the first Sequence of the first Submission and for all future Submissions.

2.5. Initial Sequence

The initial Sequence Number for all new Applications should be 0001 unless the first Sequence is a Baseline Submission. All Baseline Submissions should begin with 0000 if content was previously submitted in a non-eCTD format.

In some cases, the initial Sequence can have a much higher Sequence Number, e.g., Transfer of Application where not all Application Numbers are transferred to the Acquiring Applicant. See 3.14. Transfer of Application for more information.

2.6. Preparing the eCTD Cover Letter

The following new information shall be included in the Cover Letter in addition to what is defined in the Guidance on Therapeutic Products Registration in Singapore:

- The Application Number, Submission Number, Sequence Number and Related Sequence in the subject line, consistent with the eCTD Envelope.

  Example: e2212345A, 2212345A, Sequence 0010, Related Sequence 0008

- A description of the software used to check the files for viruses and a statement as to whether the Submission is virus free.

  Example: "The Sequence has been virus checked using SOFTWARE version VERSION and is confirmed to be virus free."

- Information about the validation including:
  - The validation tool and version / validation profile used.

    Example: SOFTWARE VERSION / Singapore 1.0.1 Profile

  - Any findings e.g. errors, warnings or possible missing documents as designated by the Document Matrix that would be expected for your specific Submission Type.

2.7. Preparing the Note to Evaluator

The purpose of the Note to Evaluator is to facilitate efficient review of the Sequence by the evaluator. If there are specific details regarding the eCTD Submission that the evaluator(s) need to be informed, it is highly recommended to provide this information in a structured document. This document may contain the following sections, as applicable:

- Files referenced at multiple locations within the backbone
- Specification adhered to
- eCTD attributes
- Hyperlink appearance and strategy
- Bookmark organisation and strategy, or deviations from recommendations
- Module organisation, e.g. the strategy for the presentation of Modules 2.3.S / 3.2.S and 2.3.P / 3.2.P
- List of documents available on request

2.8. eCTD Application Folder Naming Convention

When submitting Sequences, the Sequence Folder must be provided in an Application Folder. Use the SG eCTD ID as the eCTD Application Folder name.

Example: e20220920sg0001

The Application Folder is unique to the products within the folder and remains the root folder throughout the life cycle of the products. The Application Folder also provides flexibilities when some products contained in an Application are transferred at a later time to another Applicant. See 3.14.4.3 Transfer of Application where not all Application Numbers of an Application are Transferred ('Partial Transfer') for more information.

It is important to use the same Application Folder for all future Sequences of the Application.

Sequences already submitted should not be submitted again.

Examples:

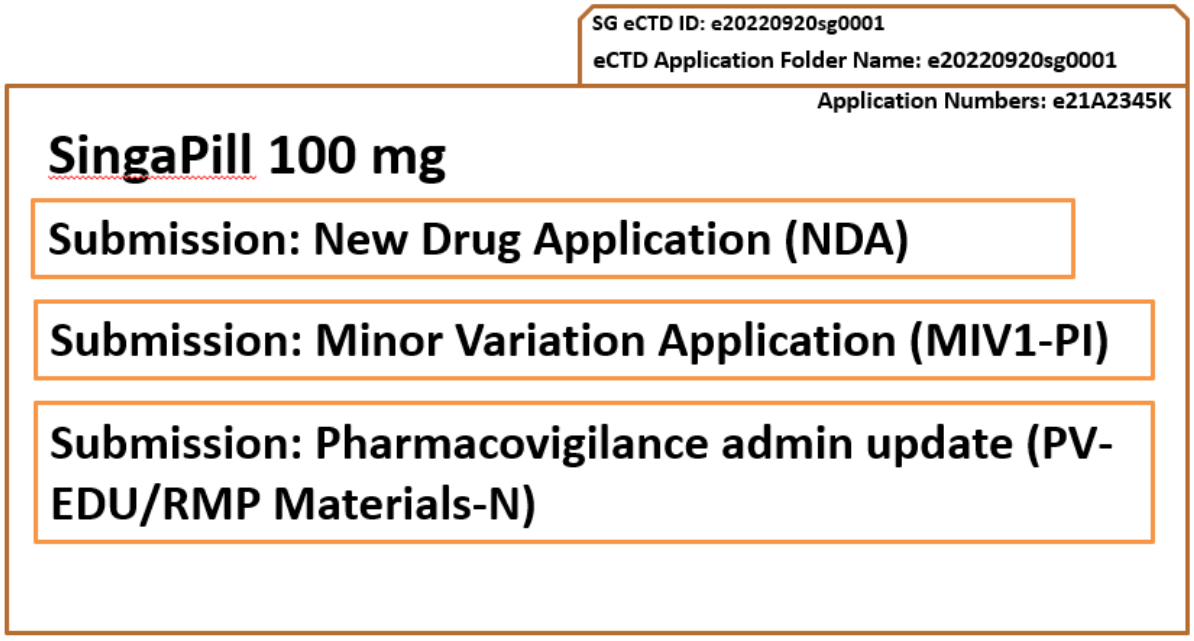

Figure 2 Example of Application Folder (Single Product Strength) Containing 3 Submissions Filed Over a Period of Time

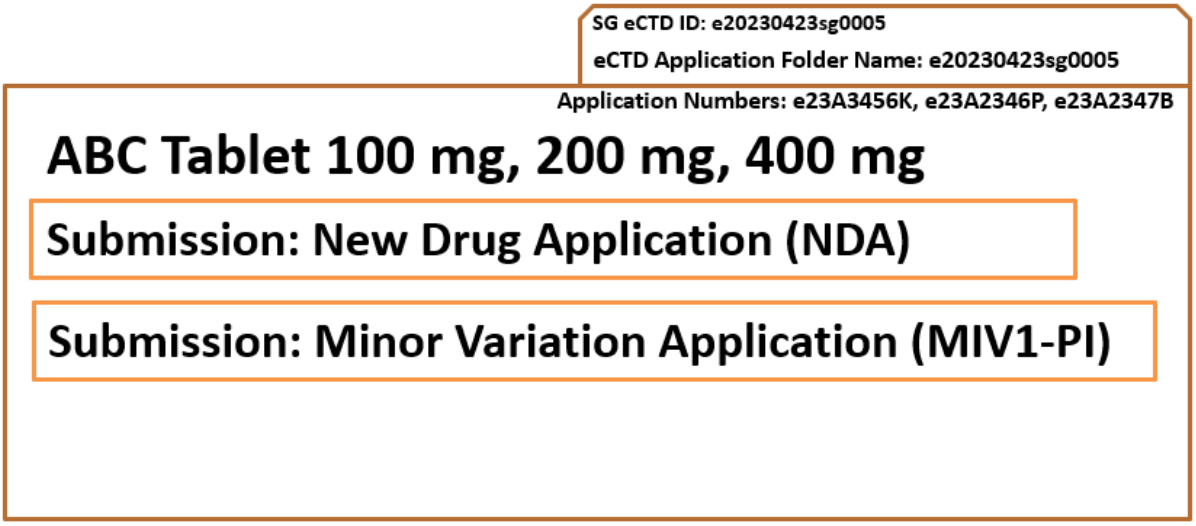

Figure 3 Example of Application Folder (Multiple Product Strengths) Containing 2 Submissions Filed Over a Period of Time

2.9. Validating the eCTD Sequence(s)

You should validate the Sequence prior to submitting it. The validation software should validate each eCTD Sequence using the SG-HSA eCTD Validation Criteria.

There are three types of eCTD validation findings:

- **ERROR** – Critical Pass/Fail finding:
  - Non-compliance will lead to rejection of the Sequence.
  - If errors are unavoidable, contact HSA before submitting the Sequence. Validation findings categorised as errors should be addressed in the Cover Letter with sufficient reasoning as to why the errors are unavoidable. Note that where automation is implemented, errors will lead to automatic rejections.
  - Refer to Sequences with Errors or Warnings for further information.
- **WARNING** – Best Practice violations:
  - Warnings should be eliminated whenever possible as this will negatively affect the evaluation process.
  - Validation findings categorised as warnings should be addressed in the Cover Letter.
  - Repeated or excessive Warnings may result in a rejection in the subsequent screening process and a request from the Authority for the Sequence to be fixed and resubmitted. Evaluation will stop in this case until a corrected Sequence is provided.
- **INFO** – Information collected about the data being submitted. This includes:
  - A list of "Possible" documents as defined in the Document Matrix that might be required in the Sequence for the Submission Type declared in the Envelope.
  - Information about Study Tagging Files submitted, etc.
  - Information about content reuse within the same Sequence, from other Sequences in the same Application and from other Applications

Validate Sequences prior to submitting them to the Authority. HSA may request for a copy of the validation report if issues arise during validation on our side.

See 5. eCTD Preparation Tools in this document for further information on suitable publishing and validation tools.

Sequences with Errors or Warnings

Evaluation will only proceed when a submitted Sequence has no Errors. Sequences with Errors will need to be corrected and resubmitted using the same Sequence Number.

For further information or to discuss specific validation Errors, please contact HSA.

If a Sequence passes validation with no errors but incurs Warnings, the Sequence will not be immediately rejected by the system. However, the Applicant should provide justifications for the Warnings in the cover letter.

If a Sequence passes validation with no Errors but excessive Warnings exist, the Sequence may be rejected in the subsequent screening process, depending on the nature and number of Warnings present or if a historical pattern has emerged with consistent excessive violations of some Warnings.

If a Sequence passes validation with no Errors or Warnings, it will be received for screening/evaluation by the Authority. Any content deficiencies discovered during the screening/evaluation process will need to be addressed in a follow-up Sequence as part of the Application life cycle.

Applicants should make every effort to provide a Sequence free of Errors and Warnings.

Feedback on Validation

The Applicant will be notified if there are any issues during the validation of the eCTD Sequence using the contact details provided in the Envelope. The validation report will be sent to the Applicant in the event the eCTD Sequence does not pass validation. The security of the email notifications received by the Applicant via the contact details provided is the responsibility of the Applicant.

2.10. Submitting your eCTD Sequence(s)

Submit your Sequences via the HSA eCTD Portal. Each Sequence Folder must be provided in a single zipped Application Folder for submission.

It is the Applicant’s obligation to ensure the security of the Application until the Application is officially received by HSA. Once received, HSA will ensure data security.

3. Singapore Regional Considerations

This section includes additional points to consider when compiling your eCTD Sequence to ensure good life cycle management of your Application and an efficient evaluation process.

3.1. File Formats

File formats refer to the accepted file type for documents within a Sequence. In most sections, the Applicant is required to provide PDF files. For files listed in Table 24 under 4.6.4 Source Documents, the source file e.g., Microsoft® (MS) Word (.doc or .docx) or Rich Text Files (RTF) should be provided either instead of the PDF or in addition to the PDF File.

Table 3 Validated PDF Requirements

Requirement	Requirement Details
Source File	Where possible, PDFs should be generated from an electronic source file – for example MS Word.
PDF Version	All PDF files, in any module, should be version 1.4 through 1.7.
External Links	No bookmarks or hyperlinks should reference a destination outside the eCTD Application(s) in the Authority repository. Links to websites and email addresses should not be provided. Only links to files found in the same Sequence, same Application or another Application already submitted are permitted. It is recommended to set the hyperlinks to open in a new window.
Inactive or Broken Links	No bookmarks or hyperlinks can be inactive or broken. All links must have a functioning valid destination.
Bookmarks	All documents with more than 10 pages that have multiple sections, tables, figures, references, etc., should contain bookmarks to aid the navigation through the document for the evaluator. Please refer to 3.3.1 Bookmarks for further information.
Relative Links	All bookmarks and hyperlinks must be relative.
Inherit Zoom	All bookmarks and hyperlinks should have a magnification setting of “Inherit Zoom”.
Single Action	All bookmarks and hyperlinks should not have multiple actions assigned (e.g., opening two different pages).
PDF Readability	PDFs must be readable and not corrupted, including documents which cannot be opened because the content is invalid or the page count is 0.
PDF Annotations	PDFs cannot contain any annotations other than bookmarks and hyperlinks.
PDF Attachments	PDF forms are allowed but should not contain any attachments.
Security	PDFs should not require passwords to open them or limit copying or printing content (except for literature references).
PDF Initial View	Documents with bookmarks should show the bookmarks pane in their initial view. The Magnification and Page Layout should be set as "default".
Fast Webview	All PDFs should have the option for “Fast Webview” activated.

For a full account of the PDF Requirements, please refer to the SG-HSA eCTD Validation Criteria section 6 PDF Analysis.

Table 4 General Source File Requirements

Requirement	Requirement Details
File Format	Source Files should be provided in MS Word or RTF unless otherwise specified. The same format as that used to create the original file is preferred.
Security	No File Security should be applied, including password protection or read-only settings.

3.1.1. Module 1

In addition to PDF, as defined in the ICH eCTD Specification, we will also accept XML, HTML and Microsoft® Word (.doc and .docx) or RTF (.rtf) where specified appropriate.

Currently, there are no structured exchange standards for content, but these may be introduced in the future for content such as application forms, product information, etc.

We may request original, source and/or processing documents e.g., Validation Reports in an external Working Documents folder located outside the official eCTD Sequence package. These files may be in various file formats and any format is accepted in the Working Documents folder. Any unusual file formats e.g., files not in Microsoft® Word, RTF, PDF, or XML related files, should be addressed in the Cover Letter. This includes Microsoft® .xls, .xlsx, .ppt and .pptx., which are the only other file formats currently accepted in Module 1.

For files listed in Table 24 under 4.6.4 Source Documents, the editable source files used to create the PDFs (MS Word or RTF) should be provided in addition to the PDFs. These shall be provided in the eCTD in the same location as the corresponding PDFs. This will allow content integrity to be secured via MD5 Checksums.

3.1.2. Module 2 to 5

In addition to the file formats defined for Modules 2 to 5 in the ICH Specification for Submission Formats for eCTD and the ICH Specifications for Study Tagging Files, we allow Microsoft® .doc, .docx, .xls, .xlsx, .ppt and .pptx., comma separated value (CSV) and plain text (TXT) files and other ASCII data files (DAT) in Modules 4 and 5 if appropriate. To accommodate submission re-use, XPT and SAS files are permitted, as outlined in 3.5. Transport Files, along with HTML files and cascading style sheets (CSS) to support presentation of study data.

3.2. Electronic Signatures

Electronic signatures will be crucial, particularly for authenticating electronic Submissions and documents. We are currently accepting:

- Digital signatures;
- Electronic or scanned signatures where the documents make up part of the checksum of an eCTD Sequence; and
- Scanned documents with wet signatures where the document has then been OCRed.

3.3. Document Navigation Aids

Bookmarks and hyperlinks should be used to assist with navigation of the Application.

3.3.1. Bookmarks

Bookmarks should be used to navigate through PDF documents and facilitate the evaluation process. We recommend that documents which have multiple headings, sections, tables, figures, references, or appendices AND more than ten (10) pages contain bookmarks. Bookmarks are not expected in Educational/RMP materials or Literature References. However, individual references should be provided as separate files and uniquely identified.

The Validation Criteria mandate a check of any documents other than Educational/RMP Materials and Literature References, which have more than ten pages but do not contain bookmarks. A list of these will be created at validation. Excessive deficiencies may lead to rejection during the screening process or complications with the evaluation of your Application, so they should be avoided.

Bookmarks are the most useful navigation aid when applied properly and are preferred over Table of Contents and Hyperlinks as they always remain up to date with the document's content.

3.3.2. Table of Contents

A Table of Contents (TOC) and/or, if appropriate, a Table of Tables, Table of Figures, etc. can be placed at the beginning of documents with multiple sections, tables, or figures.

If bookmarks are present, it is not necessary to hyperlink the TOC. Functioning bookmarks are preferred over a hyperlinked TOC. The existence of TOCs is not validated, while the existence of bookmarks is validated.

3.3.3. Document Title Pages

Document title pages are not necessary in an eCTD Application.

3.3.4. Hyperlinks

Hyperlinks can be used to aid navigation. However, the proper use of bookmarks and Leaf titles with section numbers can reduce the need for hyperlinks by encouraging the use of the eCTD index.xml and internal document navigation options. References to documents should use the Leaf titles used for those documents in the eCTD index.xml. If the reference is not done or the reference is not obvious, hyperlinks should be created.

Hyperlinks can cause confusion later in life cycle so the use of obvious hyperlinks should be avoided e.g., a reference in 2.3.S.1 to 3.2.S.1.1 Nomenclature is not necessary.

Module 3 uses a low level of granularity and is quite detailed in the definition of its content. Changes to the content are more frequent during the life cycle. Therefore, we recommend to limit the number of hyperlinks applied to Module 3 and avoid them if possible.

The structure for Module 4 and Module 5, however, is less defined and the content provided can vary greatly. Changes to the content is also less frequent during the life cycle. Therefore,

attention should be applied to hyperlinks from the summaries in Module 2 to the referenced studies in Modules 4 and 5. In particular, hyperlinks from the tabular listings of 2.7.6, the Synopsis of Individual Studies at 2.7.6 and the List of all Clinical Studies at 5.2 should be provided. Any reference in 2.4, 2.5, 2.6 or 2.7 to studies should be hyperlinked to the mentioned study.

If a reference is cited multiple times on a page, only the first instance needs to be hyperlinked.

External links, such as those leading to a website or email, should not be provided. Enough information should be provided to enable a user to search for the link if it is no longer valid.

During validation, the existence of hyperlinks in 1.0.4 Response to Input Request will be confirmed according to the Validation Criteria. Hyperlinks should be created for the sections referenced in the response document where changes were implemented.

A summary of all hyperlinks and their destinations will be created as part of the validation report. This will aid the screening process and ensure that sufficient hyperlinking has been provided.

Related Information and Guidance

ICH eCTD Specifications – Appendix 7

3.3.5. Document Granularity

For the Singapore Module 1 content, please provide documents at the lowest level of granularity defined. Do not combine defined content into a single document unless specifically directed to do so.

For Modules 2-5, please refer to the ICH M4 guidelines for the appropriate expected granularity. Please provide documents at the lowest level of granularity defined.

Note that the M4(R4) Guideline indicates a level of granularity companies can author at but asks that documents be combined into a single document for Submissions at sections 2.3.S, 2.3.P, 2.3.A and 3.2.P.2.

3.4. Empty or Missing eCTD Sections

Please provide detailed statements justifying the absence of expected data or specific CTD sections in the Cover Letter especially if the content is marked with W (Warning) in the Document Matrix for the Submission Type being submitted.

- Do not use documents with no substantive content – for example, documents that contain words like "not applicable" – in the eCTD structure. This creates unnecessary documents that are included in the life cycle and causes delays during evaluation.
- Do not provide a justification for content that is marked NV (Not Validated) in the Document Matrix for the Submission Type being submitted.
- Do not submit documents for content marked XE (Excluded: Error) or XW (Excluded: Warning) in the Document Matrix.

If excessive documents are found with no substantive content during the screening process, the sequence may be rejected although it passed initial validation.

The Document Matrix is only applicable to the initial Sequence of each Submission.

3.5. Transport Files

Program files and raw data files, e.g., SAS transport files (XPT with extension .xpt) and SAS program files (SAS with extension .sas), are not required by HSA. If provided in an eCTD Application to another agency, HSA will accept them under the principle of submission reuse. HSA does not impose any CDISC requirements (e.g., SEND, STDM, ADaM) on the datasets. The data file organisation should not be adapted for Singapore, the files should be resubmitted as is.

If Study Tagging Files (STFs) are used to organise and identify the data files in an eCTD Application to another agency, the STF(s) should also be resubmitted in Singapore with the correct study file-tags identifying the datasets.

We will collect data about the number and size of ICH E3 16.3 CRFs and non ICH E3 documents for informational purposes as part of the Validation Criteria.

Related Information and Guidance

- ICH Specifications for Study Tagging Files – Guidance on the including of studies using the STF format.
- ICH E3 – Guidance on the Structure of Clinical Study Reports.

3.6. Submission of PBRER/PSUR and RMP Reports

Periodic benefit-risk evaluation reports (PBRER) or periodic safety update reports (PSUR) and other risk management plan (RMP) reports (e.g., PV-related safety studies, reports on pregnancy prevention programmes) should be provided in Module 5 under 5.3.6 using node extensions. Please see 4.4.3. Node Extensions.

For guidance on how best to title content added to the node extensions, please see examples below and Appendix A: Best Practice Leaf Title Recommendations.

Examples of Titles:

PBRER 2023-01-01 to 2023-06-30;

RMP Report - Phase 3 Study Evaluating the Safety of Product X 2023-01-01

3.7. Updating eCTD Backbone Attributes

3.7.1. Updating ICH Attributes

XML backbone attributes should not be updated during the eCTD life cycle, as these changes can lead to complexity in the evaluation process.

For attributes where changes are more likely to occur – for example, manufacturer in 2.3.P / 3.2.P, a generic variable can be placed in the attribute field e.g., "MNF" and the manufacturer(s) represented by the variable can be declared and maintained in the Introduction. We recommend that you do not include the name of manufacturers into the XML backbone attributes.

Where multiple P sections are provided, e.g. for products which contain a vial containing a powder for injection and a vial containing the diluent, the manufacturer per P section should be tagged separately (“MNF1”, “MNF2”), even if they are initially the same manufacturer. This will allow the manufacturer for each component (P section) to be managed independently, especially in the event of future changes in manufacturer for one component but not the other.

The same approach applies when multiple S sections are provided.

3.7.2. Updating Singapore Envelope Information

The Singapore Envelope information can be updated during the life cycle as is necessary to reflect changes in the metadata, e.g., adding, removing, or changing product names.

3.8. Reusing Files

References can be made to documents provided in previous Sequences under the same Application Number(s) or under different Application Number(s). This avoids the need to resubmit a document already provided to HSA.

Do not submit the same document multiple times. Reusing content that has already been submitted and evaluated makes the evaluation process more efficient.

We accept and encourage you to reuse files when you:

- Need to submit a file several times within one Sequence.
- Need to submit a file again that has already been submitted in a previous Sequence.
- Need to submit a file again that has already been submitted in another Application Folder (SG eCTD ID).

When referencing content already used in other locations, a different title can be specified for the content in the new location independent of the title provided in the original location. References are always relative to the location where the XML file is located. For the regional content, that would be the “sg” folder. For the ICH content of Modules 2-5, that would be the Sequence Folder.

If reusing content in another location of the same Sequence, reference the location relative to the XML file location e.g., “sg” folder.

```
<m1-4-3-clinical>
 <leaf ID="Ne49d5b87f01847d4939baf67cb05a5a8" operation="new"
   xlink:href=
   "14-expert-information/141-quality/quality-chan.pdf"
   checksum="26b84c4ea4c39db30504651bdd7c2b98" checksum-type="MD5">
      <title>1.4.3 Clinical - Dr. A. Chan</title>
 </leaf>
</m1-4-3-clinical>
```

Figure 4 Referencing Content already used in the same Sequence

If reusing content provided in an earlier Sequence of the same Application, your reference will need to direct the link out of the Sequence folder and back into the Sequence where the file was provided. In the example in Figure 5, “../” is provided 3 times, i.e. directing the link out of the “sg”, “m1” and “0002” folders, then directing it back down into the “0001” folder.

```
<m1-4-3-clinical>
 <leaf ID="N9015085007574f60ae5b74fe122b20e9" operation="new"
   xlink:href=
   "../../../0001/m1/sg/14-expert-information/141-quality/quality-chong.pdf"
   checksum="e89f6b9a3824800f531b00a770f3496e" checksum-type="MD5">
      <title>1.4.3 Clinical - Dr. J. Chong</title>
 </leaf>
</m1-4-3-clinical>
```

Figure 5 Referencing Content used in an earlier Sequence of the same Application

If reusing content provided in another Application, you will need to direct the link out of the Application Folder and back into the Application Folder where the file was provided. In the example in Figure 6, “../” is provided 4 times, i.e. directing the link out of the “sg”, “m1”, “0002” and Application Folders, then directing it back down into the “e20220920sg001” Application Folder to the Sequence where the content can be found.

```
<m1-4-3-clinical>
 <leaf ID="N664d6e2d996b4a5b90fc8e2010bbf18a" operation="new"
   xlink:href=
   "../../../../e20220920sg0001/0001/m1/sg/14-expert-information/141-
quality/quality-tan.pdf"
   checksum="0a7ec7fd25f0627993b120225ca59593" checksum-type="MD5">
      <title>1.4.3 Clinical - Dr. S. Tan</title>
 </leaf>
</m1-4-3-clinical>
```

Figure 6 Referencing Content Used in Another Application Folder

Related Information and Guidance

ICH eCTD v3.2.2 Specification – Appendix 6

3.9. Handling Multiple Product Strengths of the Same Product

An Applicant may submit strength-specific Applications or combine multiple strengths of the same product in a single Application. Applicants should carefully weigh the pros and cons of combining or separating the strengths based on the product life cycle management of the product strengths.

When a new eCTD Application is provided, all strengths can be included in one eCTD Submission. An Application which comprises multiple strengths should have a single 3.2.P which covers all strengths, unless there are multiple drug components (see 3.7.1 Updating ICH Attributes). Module 1 and 3 documents which are strength-specific (i.e. 1 document per strength) should carry leaf titles which include the strength.

Example: Stability Data – 200 mg
Example: Approved-OCL-100mg

3.10. Handling Multiple Dosage Forms in a Product Range

An Applicant may submit separate Applications for each dosage form within a product range containing the same drug substance or may combine multiple dosage forms in a single Application. Applicants should carefully weigh the pros and cons of combining or separating the dosage forms based on the complexity of product life cycle management, e.g.:

- Possibility of different regulatory outcomes for different dosage forms in one Application;
- Management of variations, transfers and withdrawals involving a subset of dosage forms;
- Potentially large number of Sequences within one Application;
- Multiple files in Module 1 in certain sections within one Application, e.g. product labels.

If a new dosage form is submitted in its own Application, content reuse should be employed for documents which have already been submitted in other Applications.

For Applications which comprise multiple dosage forms, each dosage form should be added in its own Submission, i.e. an eCTD Submission for an NDA should not add more than 1 dosage form at a time. Such Applications should have separate 3.2.P sections per dosage form. When a new 3.2.P is added for a new dosage form, cross-referencing should be used to reuse previously submitted documents which are not dosage form-specific. Documents that are common to different dosage forms should not be provided more than once. Submissions for new dosage forms which do not create a separate 3.2.P will be rejected. Multiple strengths of the same dosage form should be included within a single 3.2.P. In Module 1, documents which are dosage form-specific should have the dosage form and strength reflected in the leaf title.

Example: Appendix 18A Dossier Clarification Supplement – Vial
Example: Approved-OCL-Tablet-100mg

3.11. Handling Multiple Presentations of the Same Product

An Applicant may develop multiple presentations of the same product, e.g. single-dose vials, multi-dose vials and pre-filled syringes containing the same solution for injection. It is possible to submit presentation-specific Applications or combine multiple presentations of the same dosage form in a single Application. Applicants should carefully weigh the pros and cons of combining or separating the presentations based on the product life cycle management of the presentations, as explained under 3.10 Handling Multiple Dosage Forms in a Product Range.

If a new presentation is submitted in its own Application, content reuse should be employed for documents which have already been submitted in other Applications.

For Applications which comprise multiple presentations, depending on the similarity in dossier packages, module organisation according to 3.9. Handling Multiple Product Strengths of the Same Product (i.e., a single 3.2.P section) or 3.10. Handling Multiple Dosage Forms in a Product Range (i.e., separate 3.2.P sections) may be accepted. It is important to ensure the same module organisation is used throughout the life cycle of an Application.

3.12. Baseline Submissions

Applicants may adopt eCTD submission for products and DMFs already submitted and approved by HSA prior to the introduction of eCTD. This can be achieved through a Baseline Submission for products previously submitted using the following format:

- Paper
- Other electronic files (e.g., CTD or ACTD dossier submitted in PRISM and/or CD)

Previously submitted and approved content, including Module 3 CMC data, is not required for Baseline Submissions. A Cover Letter should be provided (see Cover Letter for Baseline Submissions).

HSA does not require previously submitted and approved content to be submitted again for Baseline Submissions (Submission Type `Baseline`). However, if submitted, it should be accompanied by a declaration that the content is identical to what was previously approved by HSA. The Cover Letter for Baseline Submissions summarises the history of the Application up until the point of the Baseline.

Baseline submissions for registered products should only be provided when there is an associated regulatory activity in PRISM (i.e. MAV/MIV/Transfer). This is because the eCTD Application Number would be based on the PRISM application number provided for the associated regulatory activity (e.g. MAV/MIV/Transfer). For the Baseline Submission Number, please indicate “Other”, as explained in 2.4. The Submission Number. The first Sequence of a Baseline Submission should be 0000, as explained in 2.5. Initial Sequence.

Baseline submissions for DMFs do not need to be coordinated with applications made in PRISM, since the eCTD Application Number is based on the DMF number.

Table 5 Relevant Attributes for Baseline Submissions of Registered Therapeutic Products and DMFs (Excluding Transfer of Applications)

Relevant attributes	Required input (Product)	Required input (DMF)
eCTD Application Number	Based on PRISM application number for MAV/MIV	Based on DMF number
Submission Type	"Baseline"	"Baseline"
Submission Number	"Other"	"DMF"
Sequence Number	0000	0000

A Baseline Submission may also be required as part of a Transfer of Application process if it is a partial transfer. However, a different Sequence Number (not 0000) should be used for a partial transfer (see 3.14. Transfer of Application for details).

Cover Letter for Baseline Submissions

The purpose of the Baseline Cover Letter is to provide a record of the content used to approve the registration of the product. In addition to the information listed in 2.6. Preparing the eCTD Cover Letter, the following information should be provided in the Cover Letter for Baseline Submissions:

- The format used for the previous PRISM/CD submissions (i.e., ICH CTD/ASEAN CTD)
- When the previous regulatory activities in PRISM or updates for DMF occurred
- Indicate if multiple products (e.g., multiple strengths) will be combined into a single eCTD Application
- A summary of previous regulatory activities with key dates when possible
- Previous cover letters combined into a single bookmarked document and placed as an annex to the baseline cover letter when possible.
- A declaration that the content submitted is identical to what was previously approved by HSA, if applicable (included as an appendix to Cover Letter)

3.13. Work Grouping

At times, an Applicant may wish to submit more than one Submission in a single Sequence. In an eCTD Application, this can be done through Work Grouping. The SG-HSA Envelope is designed to allow Applicants to designate multiple Submission Types in a single Submission. Not all combinations of Submission Types, however, are allowed. Please refer to the Submission Type Matrix to understand which Submission Types can be combined with each other.

Applicants should carefully weigh the pros and cons of using Work Grouping, as it can lead to issues when:

- One of the Submissions combined in the Work Grouping is Withdrawn
- One of the Submissions combined in the Work Grouping is Rejected

All Submissions included in Work Grouping will be subject to the same processing timeline.

For more information on how to handle Withdrawals and Rejections of Submissions that were part of Work Grouping, please see 4.5.2.1 Submission Withdrawals and Work Grouping and 4.5.3.1 Rejected Submissions and Work Grouping.

Related Information and Guidance

- Submission Type Matrix – Guidance on which Submission Types can be combined in a single Submission

3.14. Transfer of Application

If products or DMFs are transferred from one Applicant to another (i.e., where there is a change of Applicant), the Application Numbers assigned to the products or DMFs will continue to apply.

The Acquiring Applicant should provide a Transfer of Application submission (Submission Type `Transfer of Application`), stating the Relinquishing Applicant in the Cover Letter and submitting a copy of the Written Confirmation of Hand-over of Dossier.

Multiple Application Numbers can be combined in a single eCTD Application – for example multiple strengths or second brand products. If only part of an Application is being transferred, the Acquiring Applicant should submit a Baseline Submission (Submission Type `Baseline`) in the next Sequence after the Transfer of Application submission, providing:

- All information, in so much as possible, required in a Baseline Submission Cover Letter in 3.12. Baseline Submissions.
- The eCTD Application Number and last Sequence Number provided by the Relinquishing Applicant which include the product now transferred to the Acquiring Applicant.

The eCTD Application is product-specific and this should be considered during any transfer process. The Relinquishing Applicant should provide all previously submitted Sequences to the Acquiring Applicant so that the Application life cycle can be continued. Even if only a partial transfer is done – i.e. not all the Application Numbers included in the Application are transferred, the entire history of the Application should be given to the Acquiring Applicant so that they have a Baseline to relate to and to base future variations on.

It is not enough for the Relinquishing Applicant to give the documentation to the Acquiring Applicant. The actual eCTD as it was submitted to the Authority should be provided so that proper life cycle management of the Application can continue. Failure to do so could result in the Acquiring Applicant facing rejections due to validation errors.

A Transfer of Application should only be undertaken when no Submissions or regulatory activities are ongoing.

3.14.1. Order of Events for Transfer of Application

The Acquiring Applicant should submit the Change of Registrant application in PRISM prior to submitting the `Transfer of Application` eCTD Submission.

The Relinquishing Applicant should submit the Change of Registrant Application in PRISM but is not required to submit the `Transfer of Application` Submission in eCTD.

3.14.2. Basic Requirements for the Relinquishing Applicant

The Relinquishing Applicant should:

- Submit Withdrawals of any open Submissions. Withdrawals will have to be done as separate Sequences, one for each Submission withdrawn. State “Transfer of Application” in the Sequence Description as the reason for withdrawal. Be sure to reverse any replacements done in those Submissions, delete any content provided as ‘New”, resubmit as “New” for any content that was “Deleted”.
- Provide any available updated post-marketing pharmacovigilance information (e.g., PBRER) requested by the Authority up to the date of transfer, irrespective of the agreed timelines with the Authority. This information should be provided as a separate Sequence under the PV-PBRER/RMP Reports Submission Type. State “Transfer of Application” in the Sequence Description as the reason for submission.

The entire eCTD including withdrawals, pharmacovigilance information and transfer Sequences must be provided to the Acquiring Applicant.

3.14.3. Basic Requirements for the Acquiring Applicant

If an Application is acquired that was previously submitted using the eCTD format, the Acquiring Applicant should continue to submit in that format, where possible.

The Acquiring Applicant must have the entire eCTD including any Sequences of withdrawals and pharmacovigilance information before they can submit their Transfer of Application Sequence.

The Acquiring Applicant should:

- Include a Cover Letter confirming the transfer
- Submit a Sequence using.
  - Submission Type: `Transfer of Application`

– Submission Number: PRISM application number for transfer (for registered products) or “DMF” (for DMF)

– Sequence Type: `Initial`

Any new Submissions and business as usual should proceed as normal in new Sequences once the transfer activities are complete.

3.14.4. Scenarios for Transfer of Application for Products

3.14.4.1. Simple Transfer of Application

In a simple transfer, there is either only 1 Application Number, or all Application Numbers included in an Application are being transferred. In addition, there are no open Submissions or regulatory activities. In this scenario, the Relinquishing Applicant should inform the Acquiring Applicant of the SG eCTD ID and Application Number(s).

Table 6 Simple Transfer of Application

Sequence Number/ PRISM submission		Activity/Task
Applicant ABC	Applicant XYZ	
0001		Applicant ABC submits eCTD Application for product with Application Number e22A2345B under SG eCTD ID 20220920sg0001.
0002		Applicant ABC submits responses to HSA’s queries and the Application is approved; the product is registered.
0003		Applicant ABC submits a `Closing Information` Sequence to update the Singapore Registration Number in the envelope and move the product labels to approved.
PRISM		Applicant ABC initiates the transfer of the product to Applicant XYZ in PRISM.
	PRISM	Applicant XYZ submits the transfer request in PRISM. PRISM issues an application number (22B2345K) to Applicant XYZ for the transfer activity.
	PRISM	The transfer of the product from Applicant ABC to Applicant XYZ is approved by HSA in PRISM.
	0004	Applicant XYZ confirms the transfer with the following eCTD Submission: SG eCTD ID: e20220920sg0001 Application Folder Name: e20220920sg0001 Application Number: e22A2345B Submission Type: `Transfer of Application`

		Submission Number: 22B2345K Sequence Type: Initial Sequence Number: 0004 Applicant XYZ should submit the documents stated in 3.14.3. to update the Application.
	0005	Applicant XYZ undertakes business as usual.

3.14.4.2. Transfer of Application with Withdrawal of Open Submissions

A transfer with open Submissions is not allowed – for example, when a regulatory activity is still under evaluation. If a transfer is done while a Submission is open, those Submissions must be withdrawn by the Relinquishing Applicant before the transfer can take place. The Relinquishing Applicant should also inform the Acquiring Applicant of the SG eCTD ID.

Table 7 Transfer of Application with Withdrawal of Open Submissions

Sequence Number/ PRISM submission		Activity/Task
Applicant ABC	**Applicant XYZ**	
0001		Applicant ABC submits eCTD Application for product with Application Number e22A2345B under SG eCTD ID 20220920sg0001.
0002		Applicant ABC submits responses to HSA's queries and the Application is approved; the product is registered.
0003		Applicant ABC submits a Closing Information Sequence to update the Singapore Registration Number in the envelope and move the product labels to approved.
0004		Applicant ABC submits a new Submission for MAV1-V with the Sequence Type Initial.
0005		Applicant ABC submits Sequence 0005 to withdraw the MAV1-V using the Sequence Type Submission Withdrawal and Related Sequence 0004.
PRISM		Applicant ABC initiates the transfer of the product to Applicant XYZ in PRISM.
	PRISM	Applicant XYZ submits the transfer request in PRISM. PRISM issues a Submission Number (22B2345K) to Applicant XYZ for the transfer activity.
	PRISM	The transfer of the product from Applicant ABC to Applicant XYZ is approved by HSA in PRISM.

0006	Applicant XYZ confirms the transfer with the following eCTD Submission: SG eCTD ID: e20220920sg0001 Application Folder Name: e20220920sg0001 Application Number: e22A2345B Submission Type: `Transfer of Application` Submission Number: 22B2345K Sequence Type: `Initial` Sequence Number: 0006 Applicant XYZ should submit the documents stated in 3.14.3. to update the Application.
0007	Applicant XYZ undertakes business as usual.

3.14.4.3. Transfer of Application where not all Application Numbers of an Application are Transferred ('Partial Transfer')

If multiple Application Numbers have been grouped into a single Application, it is possible that the Applicant may want to transfer a subset of the Application Numbers but not all of them. Examples of this scenario include the transfer of a subset of the full range of product strengths or the transfer of second-brand products to separate them from the originator products.

In this situation, the Relinquishing Applicant will continue the original Application, adjusting the Envelope information to exclude the products that have been transferred. The Acquiring Applicant, however, will need to request a new SG eCTD ID from the HSA eCTD Portal and submit a Baseline Submission providing information about the Application as provided by the Relinquishing Applicant.

The Application Folder containing the Application must be unique. The Relinquishing Applicant must continue to use the existing Application Folder for the remaining products. The Acquiring Application must create a new Application Folder using the new SG eCTD ID for the product acquired.

Table 8 Transfer of Application where not all Application Numbers of an Application are Transferred ('Partial Transfer')

Sequence Number/ PRISM submission		Activity/Task
Applicant ABC	**Applicant XYZ**	
0001		Applicant ABC submits eCTD Application for products with Application Numbers e22A2345B and e22A2346C. The Application Folder e20220727sg0001 is used.

0002		Applicant ABC submits responses to HSA's queries and the Application is approved; products are registered.
0003		Applicant ABC submits a `Closing Information` Sequence to update the Singapore Registration Number in the envelope and move the product labels to approved.
PRISM		Applicant ABC initiates the transfer of product e22A2345B to Applicant XYZ in PRISM but not e22A2346C.
	PRISM	Applicant XYZ submits the transfer request in PRISM. The PRISM application number for the transfer is 23B2345K.
	PRISM	The transfer of the product e22A2345B from Applicant ABC to Applicant XYZ is approved by HSA in PRISM.
	0004	Applicant XYZ obtains a new SG eCTD ID (e20230925sg0005) from the HSA eCTD Portal and submits a new eCTD Application: Application Folder Name: e20230925sg0005 Application Number: e22A2345B Submission Type: `Transfer of Application` Submission Number: 23B2345K Sequence Type: `Initial` Sequence Number: 0004 To confirm the transfer, Applicant XYZ should also update the Application with the documents stated in 3.14.3.
	0005	Applicant XYZ submits: Application Folder Name: e20230925sg0005 Application Number: e22A2345B Submission Type: `Baseline` Submission Number: Other Sequence Type: `Initial` Sequence Number: 0005 Applicant XYZ also submits the Baseline Submission Cover Letter
	0006	Applicant XYZ undertakes business as usual.

0004	Applicant ABC undertakes business as usual but only lists Application Number e22A2346C in the Envelope. The Application Folder continues to be e20220727sg0001.

4. Singapore Module 1 General Architecture

4.1. Backbone File for Singapore Module 1

The Singapore Module 1 eCTD backbone file is comprised of:

- a fixed eXtensible Markup Language (XML) root Element;
- the eCTD Envelope Elements; and
- the eCTD Heading Elements describing the sections where files are to be provided.

4.1.1. Creating the Module 1 eCTD backbone file

To create the Singapore Module 1 backbone file for a given Sequence, use an authenticated eCTD preparation software compliant to the following:

1. Create an XML file containing the standard XML Root Element with the appropriate XML declaration.
2. Create the Envelope Elements containing the appropriate metadata values describing the Application, Submission, Sequence and Contact details.
3. Create content as needed for the Sequence:
    a. Module 1 Heading Elements – organising the Singapore Module 1 in accordance with the Specifications.
    b. Leaf Element – reference to each file being submitted along with other information such as eCTD checksum and life cycle information.
4. Name the Singapore Module 1 eCTD backbone file `sg-regional.xml` and place it in the sg subfolder within Module 1, i.e., within the m1 subfolder of the Sequence.
5. Validate the resulting backbone using a suitable eCTD validation tool.
6. Fix any errors and warnings.
7. Validate the Sequence again until an acceptable validation report is produced.
8. Follow the process to submit your Sequence.

4.1.2. Stylesheets

In addition to the ICH standard stylesheet (ectd-2-0.xsl), the Singapore Module 1 is also provided with a standard stylesheet (sg-regional.xsl). Each stylesheet can be used to view the respective content (i.e., ICH or regional backbone file) in a browser, rendered dynamically, or it can be used to create a static HTML rendition of each backbone. The renditions can be used to:

- View content
- Display the complete Module 1 table of contents, i.e., all sections, irrespective of whether files are present in those sections
- Display the ICH Module 2-5 table of contents as provided in the ICH backbone

- Enable you to use a browser to open the content

eCTD Applications must be submitted with the stylesheets in the util\style folder. Existence of the stylesheet as well as the checksum of each stylesheet is checked during the validation process.

4.1.3. Optional HTML File

An HTML rendition of the ICH and/or Regional backbone can be provided in the eCTD folder. If provided, the HTML renditions should be created using the stylesheets provided in the "util" folder and placed beside the corresponding backbone file. Only one rendition of each backbone file is permitted (sg-regional.html, index.html). When rendered using the sg-regional stylesheet, the sg-regional.html will display the md5 checksum of the sg-regional.xml. The checksum will be validated (severity: Informational). HTML renditions will not be reviewed.

4.2. XML Root Element

All Singapore Module 1 backbone files will contain the standard XML root element.

The required text includes an XML declaration and the root element `sg-hsa_ectd` with its attributes linking this XML file to the XML definition.

The line breaks inside of the `sg-hsa_ectd` Element as shown in the following two excerpts are not mandatory.

```
<?xml version="1.0" encoding="UTF-8"?>

<sg-hsa_ectd schema-version="1.0"
        xmlns="sg-hsa_ectd"
        xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
        xsi:schemaLocation="sg-hsa_ectd ../../util/dtd/sg-regional.xsd"
        xmlns:xlink="http://www.w3.org/1999/xlink" >
```

Figure 7 XML Root Element

4.3. Envelope Elements

The XML Envelope is a key part of a regional eCTD Specification. Each Element enables the correct identification of the administrative information needed by the receiving Authority to process the Application over time.

The Envelope information is provided for automated Authority purposes and is broken down into the following sections:

- **Application** – High level Application information valid for multiple if not all Submissions.
- **Submission** – Information relating to the Submission (regulatory activity) that is being submitted.
- **Sequence** – Information relating to the Sequence that is being submitted.
- **Contact Details** – Information on who should be contacted should questions arise during the evaluation process.

Each Envelope Element is subject to a defined Constraint which are:

- **Mandatory** – The Element must exist to avoid validation errors.
- **Optional** – The Element should be excluded when it is not relevant to the Application. If included, it will be subjected to validation.

Each Envelope Element is subject to restrictions on Occurrences which are:

- **Single** – The Element can only occur once within the restraints of the parent Element in which it occurs.
- **Multiple** – The Element can occur multiple times within the restraints of the parent Element in which it occurs.
- **Unique** – The Element can occur multiple times within the restraints of the parent Element in which it occurs, however the values associated with the Element should be unique within the restraints.

Values for some Envelope elements are restricted with a Defined List. Please see 4.3.3. The Defined Lists for more information .

4.3.1. Envelope Overview

Table 9 Overview of the Envelope Elements

Element	Description	Constraint	Occurrence	Defined List*
sg-envelope	Root element for envelope metadata			
application	Parent element for Application metadata indicating Type	Mandatory	Single	X
sg-ectd-id	SG eCTD ID	Mandatory	Single	-
application-number	Application Number(s)	Mandatory	Unique	-
inn	INN[2]	Mandatory	Unique	
product-type	Product Type	Mandatory	Single	X
dmf-number	DMF Number	Optional	Unique	
pmf-number	PMF Number	Optional	Unique	
proprietary-name	Proprietary Name(s)	Mandatory	Unique	
sin-number	Singapore Registration Number	Optional	Unique	
submission	Parent element for Submission metadata indicating Type	Mandatory	Unique	X
submission-number	Submission Number	Mandatory	Unique	
sequence	Parent element for Sequence metadata indicating Type	Mandatory	Single	X
sequence-description	Sequence Description	Mandatory	Single	
sequence-date	Sequence Date	Mandatory	Single	
sequence-number	Sequence Number	Mandatory	Single	
related-sequence-number	Related Sequence Number	Mandatory	Single	
contact	Parent element for Contact metadata indicating Type	Mandatory	Multiple	X
contact-name	Contact Name	Mandatory	Single	
contact-email	Contact Email	Mandatory	Single	
contact-phone	Contact Phone	Optional	Single	

[2] International Non-proprietary Name(s)

4.3.2. Submitting Multiple Values in the Envelope

Please provide a separate Element for each entry when submitting multiple values for Envelope Elements such as Application Number, INN, DMF Number, PMF Number, Proprietary Name, SIN Number, Submission Type, Submission Number and Contact Type.

Figure 8 provides an example of an Envelope pertaining to an initial Sequence of a Submission comprising a Minor Variation-1 (Clinical PI Changes).

```
<sg-envelope>
      <application code-version="1.0" code="app-type-1">
         <sg-ectd-id>e20201230sg0001</sg-ectd-id>
         <application-number>e21A2345K</application-number>
         <application-number>e21A2346P</application-number>
         <application-number>e21A2347B</application-number>
         <inn>rosuvastatin</inn>
         <inn>ezetimibe</inn>
         <product-type code-version="1.0" code="prod-type-1" />
         <sin-number>SIN12345P</sin-number>
         <sin-number>SIN12346P</sin-number>
         <sin-number>SIN12347P</sin-number>
         <dmf-number>015:01</dmf-number>
         <dmf-number>015:688</dmf-number>
         <proprietary-name>singaPill Tablet 10mg/10mg</proprietary-name>
         <proprietary-name>singaPill Tablet 20mg/10mg</proprietary-name>
         <proprietary-name>singaPill Tablet 40mg/10mg</proprietary-name>
      </application>

      <submission code-version="1.0" code="sub-type-8">
         <submission-number>2212378K</sub-number>
         <submission-number>2212379P</sub-number>
         <submission-number>2212380B</sub-number>
      </submission>

      <sequence code-version="1.0" code="seq-type-1">
         <sequence-description>PI Update</sequence-description>
         <sequence-date>2022-07-20</sequence-date>
         <sequence-number>0010</sequence-number>
         <related-sequence-number>0010</related-sequence-number>
      </sequence>

      <contact code-version="1.0" code="contact-type-1">
         <contact-name>Dr. Sarah Tan</contact-name>
         <contact-email>sarah.tan@pharma-inc.co.sg</contact-email>
         <contact-phone>+65 1234 5678</contact-phone>
      </contact>
      <contact code-version="1.0" code="contact-type-3">
         <contact-name>Aiden Chan</contact-name>
         <contact-email>aiden.chan@pharma-inc.co.sg</contact-email>
         <contact-phone>+65 1234 5679</contact-phone>
      </contact>
</sg-envelope>
```

Figure 8 Sample Code for Submitting Multiple Values in the Envelope

4.3.3. The Defined Lists

The defined lists are separate XML files maintained by Singapore containing a standard set of codes for the corresponding Envelope Element. The Defined lists are maintained independent of the Specifications and can be updated at any time without the need to update the Specifications.

The XML file specifies:

- a `number` for each version,
- a `valid-from` for each version,
- an `expired` date (if applicable).

```
<versions>
   <version number="1.0" valid-from="2023-01-01" expired="2024-06-30"/>
   <version number="2.0" valid-from="2024-01-01" expired="2024-11-30"/>
   <version number="2.1" valid-from="2024-05-20"/>
</versions>
```

Figure 9 Defined List Version Validity

Each coded value has:

- a code which is set and will not change over time;
- its own `valid-from-version` assigned, which defines the first version of the file where this code is valid;
- its own `valid-to-version` assigned if applicable, which defines the last version of the file where the code is valid; and
- a description that correlates to the assigned code. The description can be edited by HSA over time should there be a need to change the terminology.

```
<item code="sub-type-14" valid-from-version="1.0" valid-to-version="2.0">PV-EDU/RMP
Materials</item>
```

Figure 10 Defined List Code Validity

Provide the `code` attribute value from the appropriate Element in the `sg-regional.xml` file. See the example XML code under Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

Be sure the codes used are still valid in the current version of the defined list. We will validate Sequences to ensure that codes are valid according to the version information and the Sequence Date of Submission provided in the Envelope.

The defined lists are stored on the Singapore HSA website (https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions). Changes to the files will be made independent to these Specifications. It is expected that validation tools will dynamically use the lists on the website for validation. Versions will remain valid for 6 months after they have been superseded.

Related Information and Guidance

- eCTD Defined Lists – Official defined lists for the Singapore eCTD Elements

4.3.4. Envelope Attributes

4.3.4.1. Application Type

The Application element section contains all the Application-related information that is not related to a specific Submission or Sequence. Only one Application element section can be provided.

Application Type is a coded list. The Application Type should be indicated for the Application.

Example: app-type-1

```
<application code-version="1.0" code="app-type-1">
```

Figure 11 Envelope Element: Application Type

Related Information and Guidance

- application-type – Official defined list for Application Type

4.3.4.2. SG eCTD ID

A unique identifier issued by HSA via the HSA eCTD Portal.

The same SG eCTD ID will be used for all Sequences of an eCTD Application and cannot ever be changed.

Example: e20201230sg0001

```
<sg-ectd-id>e20201230sg0001</sg-ectd-id>
```

Figure 12 Envelope Element: SG eCTD ID

4.3.4.3. Application Number

Each product or DMF will be assigned a unique Application Number, which is either derived from PRISM or from the DMF number (see 2.3. The Application Number for more information on Application Numbers).

Multiple Application Numbers can be included in an eCTD Application e.g., it is appropriate to combine different strengths, different presentations, and any second brand products in a single Application. It may also be possible to combine different pharmaceutical forms in a single Application (see sections 3.9, 3.10 and 3.11).

Hence, an Application Number will be required for:

- Each strength for products with multiple strengths
- Each second brand product, also for all strengths of the second brand product
- Each strength of every dosage form or presentation (if there are multiple forms or presentations in the Application).

Table 10 Example of when Multiple Application Numbers are Used for Different Strengths and Second Brand Products in One Application

Product	Strength	Form	Application Number
singaPill	200mg	Film Coated Tablet	e22A2341A
singaPill	100mg	Film Coated Tablet	e22A2342D
singaPill	400mg	Film Coated Tablet	e22A2343G
genPill*	200mg	Film Coated Tablet	e24A2344J
genPill*	100mg	Film Coated Tablet	e24A2345L
genPill*	400mg	Film Coated Tablet	e24A2346P

* In this example, genPill is a second brand product of singaPill. The products are identical, but an additional product name is being registered.

Example: e22A2345B

```
<application-number>e22A2345B</application-number>
```

Figure 13 Envelope Element: Application Number

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

If a Submission only pertains to a subset of products within an existing Application, the Envelope should only contain the Application Numbers relevant to the Submission. The Application Number(s) of the products not involved in the Submission should not be included.

During the life cycle of an eCTD Application, a product may be added or removed from the eCTD Application. When a new Sequence is submitted, the Application Numbers stated in the Envelope should accurately reflect the products included in the eCTD Application.

4.3.4.4. International Non-proprietary Name(s) (INN)

The recognised International Non-proprietary Name(s) should be given. It should only be written in lower-case letters and provided exactly as listed as INN without abbreviations.

Example: amoxicillin

```
<inn>amoxicillin</inn>
```

Figure 14 Envelope Element: INN

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

4.3.4.5. Product Type

Product Type is a coded list. The type of product being submitted e.g., Chemical, Biological or Biosimilar must be declared. For a DMF eCTD application, “DMF” should be selected as the product type.

Example (Chemical): prod-type-1

```
<product-type code-version="1.0" code="prod-type-1" />
```

Figure 15 Envelope Element: Product Type

4.3.4.6. DMF Number

If a DMF is referenced in the current eCTD Application, the DMF Number issued by HSA should be included. Please note that a corresponding Letter of Access should be provided in section 1.5.3.1.

This is an optional field – if a DMF is not applicable for the Application, this element should be excluded from the Envelope, as entering ‘Nil’ may result in validation failure.

```
<dmf-number>015:1234</dmf-number>
```

Figure 16 Envelope Element: DMF Number

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

4.3.4.7. PMF Number

If a Plasma Master File (PMF) is reference in the current eCTD application, the PMF Number issued by HSA should be added. Please note that a corresponding Letter of Access should be provided in section 1.5.3.2.

This is an optional field – if a PMF is not applicable for the Application, this element should be excluded from the Envelope, as entering ‘Nil’ may result in validation failure.

```
<pmf-number>005:12</pmf-number>
```

Figure 17 Envelope Element: PMF Number

4.3.4.8. Proprietary Name(s)

The name as proposed or registered in PRISM.

For Drug Master Files, insert drug substance name and DMF holder name.

Example: singaPill Tablet 10mg/10mg

Example: amoxicillin DMF Pharma

```
<proprietary-name> singaPill Tablet 10mg/10mg </proprietary-name>
```

Figure 18 Envelope Element: Proprietary Names

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

If a Submission only pertains to a subset of products within an existing Application, the Envelope should only contain the Proprietary Names relevant to the Submission. The Proprietary Name(s) of the products not involved in the Submission should not be included.

4.3.4.9. Singapore Registration Number

The Singapore Registration Number should be provided for all sequence types of registered products. It should only be written in upper-case letters. If multiple registration numbers are associated with the eCTD Application, all registration numbers should be provided.

If the product is not yet registered by HSA, i.e., for NDA, NDA-V, GDA and GDA-V/CECA Submissions, the Singapore Registration Number should not be provided (and the element should be absent from the Envelope) except in a 'Closing Information' Sequence (see 4.3.4.12. Sequence Type). Including the element while entering 'Nil' may result in validation failure.

When the product type is DMF (product-type-4), the SIN number is optional.

```
<sin-number>SIN12345P</sin-number>
```

Figure 19 Envelope Element: Singapore Registration Number

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

If a Submission only pertains to a subset of products within an existing Application, the Envelope should only contain the Singapore Registration Number relevant to the Submission. The Singapore Registration Number of the product(s) not involved in the Submission should not be included.

4.3.4.10. Submission Type

The Submission Element section contains all the Submission-related information that is not related to a specific Sequence. Multiple Submission Element sections can be provided if the combination is allowed in the Submission Type Matrix.

Submission Type is a coded list. The Submission Type must be indicated for the Submission Element indicating the type of regulatory activities being undertaken with the Submission. If multiple products are involved in a Submission Type, then all associated Submission Numbers should be listed within the same Submission Type section.

When multiple Submissions of the same Submission Type are combined, multiple Submission Numbers should be listed within a single Submission and the Submission Type should only be included in the envelope once.

When multiple Submissions are listed, follow-up Sequences (responses, supplemental information and/or withdrawals) should only list the Submissions that are directly affected by the content being submitted in the follow-up Sequence. For example, if a MIV1-PI Submission and MIV2-N Submission are combined in the first Sequence but a response was only required for the MIV1-PI, the MIV2-N Submission would not be listed in the Envelope of the follow-up Sequence.

Once a Submission has started, it is not possible to combine new Submissions with the responses of existing Submissions.

We recommend avoiding combining Submissions in a single Sequence whenever possible, however combinations in line with the Submission Type Matrix will be allowed.

Example: sub-type-1

```
<submission code-version="1.0" code="sub-type-1">
```

Figure 20 Envelope Element: Submission Type

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

Related Information and Guidance

- submission-type – Official defined list for Submission Type
- Submission Type Matrix – A summary of the allowed combinations of Submission Types in a single Sequence.

4.3.4.11. Submission Number(s)

The Submission Number(s) applicable to the Sequence being submitted should be indicated.

See The Submission Number for more information on Submission Numbers.

If appropriate, multiple Submission Numbers can be provided for a particular Submission e.g., when the same action is taken on all strengths.

Example: 22A1234K

Example: DMF

Example: PV

Example: Other

```
<submission-number>22A2345K</submission-number>
```

Figure 21 Envelope Element: Submission Number

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

4.3.4.12. Sequence Type

The Sequence Element section contains all the Sequence-related information. It identifies what is happening to the Submission with the Sequence being submitted. Only one Sequence Element section can be specified per Sequence.

Sequence Type is a coded list. The first Sequence of a Submission must always be `Initial`. Follow-up Sequences should indicate whether it is a `Response`, `Supplementary Information`, `Closing Information` or a `Submission Withdrawal`.

Please note that the `Closing Information` Sequence Type should only be used to provide information under an Approved situation and only with Module 1 content. The Singapore Registration Number should be provided in a `Closing Information` Sequence after registration has been granted upon approval of an NDA/NDA-V or GDA/GDA-V/CECA Submission.

Example (Initial): seq-type-1

```
<sequence code-version= "1.0" code="seq-type-1">
```

Figure 22 Envelope Element: Sequence Type

Related Information and Guidance

- sequence-type – Official defined list for Sequence Type

4.3.4.13. Sequence Description

The Sequence Description element gives the Applicant the opportunity to better describe what is being done in the Sequence. The following should be considered when providing a Sequence Description

- **Make it Short, Precise and Distinguishing** – Avoid extensive descriptions, which would be more appropriate in the Cover Letter and/or Note to Evaluator. Think of the description as a categorisation of the Sequence that will help distinguish it from a long list of Sequences provided. It is recommended to keep it within 128 characters.

- **Avoid Repeating Information** – Do not indicate the Submission Type or the Sequence Type in the Description.
- **For Initial Sequence Types** – Provide more detail about the Submission Type.
- **For Supplemental Information** – Provide information on what is being provided.
- **For Responses** – Indicate the date of the Input Request e.g., "*Response to 2022-11-20 IR".*
- **For Withdrawals** – Indicate a brief reason for withdrawal.

Example (NDA – Initial): New Application

Example (GDA – Response): Response to 2021-11-20 LOQ

Example (MAV1 – Initial): Indication Psoriasis to be added

```
<sequence-description>Editorial Changes to Blister Pack</sequence-description>
```

Figure 23 Envelope Element: Sequence Description

4.3.4.14. Sequence Date

The Sequence Date is a date field indicating the planned submission date of the Sequence (format: yyyy-mm-dd). This date should correlate as closely as possible with the date on the Cover Letter and in the Application Form but is not necessary to be identical. The Sequence Date is mainly used to ensure the validity of the codes used from the Defined Lists. Based on the Sequence Date, the validation tools checks that the code used is valid at the time of the Sequence Date.

Sequence Dates will be validated to ensure they indicate a date within 30 days of the date of validation. Dates outside this time period will cause validation warnings which must be addressed in the Cover Letter.

Example: 2024-05-20

```
<sequence-date>2024-05-20</sequence-date>
```

Figure 24 Envelope Element: Sequence Date

4.3.4.15. Sequence Number

Four-digit number matching the Sequence folder being submitted.

New Applications with Submissions starting with a "`New Drug Application…`", "`Generic Drug Application…`" or "`DMF`" Submission Type should start with the Sequence 0001.

Baseline Submissions should start with the Sequence 0000, except when associated with a partial transfer situation (see 3.14.4. Scenarios for Transfer of Application for Products).

Transfer of Application should start on the Sequence after the last Sequence the previous Applicant submitted for the product.

Example: 0011

```
<sequence-number>0011</sequence-number>
```

Figure 25 Envelope Element: Sequence Number

4.3.4.16. Related Sequence Number

The Related Sequence Number is used to group Sequences belonging to the same Submission. This enables us to easily evaluate Sequences associated with a particular Submission.

All Sequences that belong to a specific Submission should contain the same four-digit number in the Related Sequence Number field as demonstrated in the table:

Table 11 Related Sequence Explained

Sequence Number	Related Sequence Number	Submission Type	Sequence Type
0001	**0001**	NDA	Initial
0002	**0001**	NDA	Supplementary Information
0003	**0001**	NDA	Response
0004	**0001**	NDA	Closing Information
0005	**0005**	MAV1-V	Initial
0006	**0006**	MIV2-DnT	Initial
0007	**0007**	MIV1-PI	Initial
0008	**0005**	MAV1-V	Supplementary Information
0009	**0005**	MAV1-V	Response
0010	**0005**	MAV1-V	Response
0011	**0007**	MIV1-PI	Response

Each Initial Sequence of a Submission will reference itself.

Each follow-up Sequence of a Submission will reference the Initial Sequence of that Submission.

Example: 0001

```
<related-sequence-number>0001</related-sequence-number>
```

Figure 26 Envelope Element: Related Sequence Number

4.3.4.17. Contact Type

The Contact element section contains all the Contact related information for a particular contact. Multiple contacts may be provided in the Envelope. The Contact Name and Contact Email must be provided for each contact, along with the Type of contact. The Contact Phone is requested for each contact, but it is optional. At least one Agent Singapore contact must be provided and should preferably be the same person as the PRISM Applicant.

Contact information will only be used to communicate the validation outcome.

Contact Type is a coded list. The Contact Type must be indicated for the Contact element. The code should be indicated in the Envelope.

Example (Regulatory Contact): contact-type-1

```
<contact code-version="1.0" code="contact-type-1">
```

Figure 27 Envelope Element: Contact Type

See the example XML code in Figure 8 Sample Code for Submitting Multiple Values in the Envelope.

Related Information and Guidance

- contact-type – Official defined list for Contact Type

4.3.4.18. Contact Name

A Contact Name must be provided for each Contact Type included. -

Example: Dr. Sarah Tan

```
<contact-name>Dr. Sarah Tan</contact-name>
```

Figure 28 Envelope Element: Contact Name

4.3.4.19. Contact Email

A Contact Email must be provided for each Contact Type included.

Example: sarah.tan@pharma-inc.co.sg

```
<contact-email>sarah.tan@pharma-inc.co.sg</contact-email>
```

Figure 29 Envelope Element: Contact Email

4.3.4.20. Contact Phone

A Contact Phone number can be provided for each Contact Type but is not mandatory. While this is an optional field, we encourage the Applicant to provide telephone numbers whenever possible. If it is not being provided, this element should be excluded from the Envelope, as entering 'Nil' may result in validation failure.

Example: +65 1234 5678

```
<contact-phone>+65 1234 5678</contact-phone>
```

Figure 30 Envelope Element: Contact Phone

4.4. Heading and Leaf Elements

4.4.1. Module 1 Heading Elements

The next 10 tables list the Heading elements of the Singapore eCTD Module 1.

Content under the following Headings should be provided when required, as defined in the Document Matrix.

Please refer to the Guidance on Therapeutic Products Registration in Singapore and HSA eCTD website for the expected information under each of these sections. Please note that some sections may not be mandatory. We encourage to regularly check for updates to the Document Matrix.

Please refer to Appendix A: Best Practice Leaf Title Recommendations for guidance on how to title content added to the defined sections.

Table 12 Heading Elements 1.0 – Correspondence

Section ID	Title	XML-Element
1.0	**Correspondence**	**m1-0-correspondence**
1.0.1	Cover Letter	m1-0-1-cover-letter
1.0.2	Note to Evaluator	m1-0-2-note-evaluator
1.0.3	Correspondence with HSA	m1-0-3-hsa-correspondence
1.0.4	Response to Input Request	m1-0-4-response-hsa
1.0.5	Meeting Information	m1-0-5-meeting-info

Table 13 Heading Elements 1.2 – Administrative Information

Section ID	Title	XML-Element
1.2	**Administrative Information**	**m1-2-admin-info**
1.2.1	Application Forms	m1-2-1-app-form
1.2.2	Checklists	m1-2-2-checklists
1.2.2.1	Appendix 2a Checklist	m1-2-2-1-2a

1.2.2.2	Appendix 2b Checklist	m1-2-2-2-2b
1.2.2.3	Appendix 13a/14a Checklist	m1-2-2-3-13a-14a
1.2.2.4	Appendix 13b/14b Checklist	m1-2-2-4-13b-14b
1.2.2.5	Appendix 13c/14c Checklist	m1-2-2-5-13c-14c
1.2.3	Annexes	m1-2-3-annexes
1.2.3.1	Letter of Authorisation from Product Owner	m1-2-3-1-loa
1.2.3.2	Change in Applicant	m1-2-3-2-change-applicant
1.2.3.2.1	Letter of Authorisation from Product Owner to New Registrant	m1-2-3-2-1-change-loa
1.2.3.2.2	Written Confirmation of Hand-over of Dossier	m1-2-3-2-2-confirmation-of-hand-over
1.2.3.3	Declaration for Verification or Verification-CECA	m1-2-3-3-decl-verif
1.2.3.4	Patent Declaration	m1-2-3-4-pat-declaration
1.2.3.4.1	Patent Declaration Form	m1-2-3-4-1-pat-decl-form
1.2.3.4.2	Evidence of Authorisation	m1-2-3-4-2-pat-evidence-auth
1.2.4	Table of Summary of Changes	m1-2-4-summary-of-changes
1.2.A	Additional Administrative Information	m1-2-a-additional-admin-info

Table 14 Heading Element 1.3 – Product Information

Section ID	Title	XML-Element
1.3	**Product Information**	**m1-3-product-info**
1.3.1	Outer Carton Labels (OCL)	m1-3-1-ocl
1.3.1.1	Approved - OCL	m1-3-1-1-ocl-approved
1.3.1.2	Clean Proposed - OCL	m1-3-1-2-ocl-clean
1.3.1.3	Annotated - OCL	m1-3-1-3-ocl-annotated
1.3.2	Inner/Blister Labels (IBL)	m1-3-2-ibl
1.3.2.1	Approved - IBL	m1-3-2-1-ibl-approved
1.3.2.2	Clean Proposed - IBL	m1-3-2-2-ibl-clean
1.3.2.3	Annotated - IBL	m1-3-2-3-ibl-annotated
1.3.3	Package Insert (PI)	m1-3-3-pi

1.3.3.1	Approved - PI	m1-3-3-1-pi-approved
1.3.3.2	Clean Proposed - PI	m1-3-3-2-pi-clean
1.3.3.3	Annotated - PI	m1-3-3-3-pi-annotated
1.3.4	Patient Information Leaflet (PIL)	m1-3-4-pil
1.3.4.1	Approved - PIL	m1-3-4-1-pil-approved
1.3.4.2	Clean Proposed - PIL	m1-3-4-2-pil-clean
1.3.4.3	Annotated - PIL	m1-3-4-3-pil-annotated
1.3.5	Approved Foreign Labelling (SPC/PI/PIL)	m1-3-5-foreign-label
1.3.5.1	SPC/PI/PIL - Reference Agency	m1-3-5-1-ref-foreign-label
1.3.5.2	SPC/PI/PIL - Proof of Approval Agency	m1-3-5-2-proof-approval-foreign-label
1.3.5.3	SPC/PI/PIL - Other Agency	m1-3-5-3-other-foreign-label
1.3.6	Declarations on Foreign Text/Braille	m1-3-6-decl-foreign

Table 15 Heading Elements 1.4 – Information about the Experts

Section ID	Title	XML-Element
1.4	**Information about the Experts**	**m1-4-info-experts**
1.4.1	Quality	m1-4-1-quality
1.4.2	Nonclinical	m1-4-2-nonclinical
1.4.3	Clinical	m1-4-3-clinical

Table 16 Heading Elements 1.5 – Master Files and Certificates of Suitability

Section ID	Title	XML-Element
1.5	**Master Files and Certificates of Suitability**	**m1-5-master-files**
1.5.1	DMF Acknowledgement Email	m1-5-1-dmf-email
1.5.2	Letter of Access	m1-5-2-loaccess
1.5.2.1	DMF Letter of Access	m1-5-2-1-dmf-loaccess
1.5.2.2	PMF Letter of Access	m1-5-2-2-pmf-loaccess

1.5.3	EMA Certificate for Plasma Master File (PMF)	m1-5-3-ema-pmf
1.5.4	Certificate of Suitability (CEP)	m1-5-4-cep

Table 17 Heading Elements 1.6 – Environmental Risk Assessment

Section ID	Title	XML-Element
1.6	**Environmental Risk Assessment**	**m1-6-env-risk-assessment**
1.6.1	Non-GMO	m1-6-1-non-gmo
1.6.2	GMO	m1-6-2-gmo

Table 18 Heading Elements 1.7 – Good Manufacturing Practice

Section ID	Title	XML-Element
1.7	**Good Manufacturing Practice**	**m1-7-gmp**
1.7.1	GMP Certificates or Proof of GMP Compliance	m1-7-1-gmp-certificates
1.7.1.1	Drug Substance Manufacturers	m1-7-1-1-drug-substance
1.7.1.2	Finished Pharmaceutical Product (FPP) Manufacturers	m1-7-1-2-fpp
1.7.1.3	Batch Releaser	m1-7-1-3-batch-releaser
1.7.2	Description of Batch Numbering System	m1-7-2-desc-batch-no-sys
1.7.3	HSA GMP Conformity Assessment Application	m1-7-3-gmp-conform-appl
1.7.3.1	Application for GMP Evidence Evaluation	m1-7-3-1-gmp-deva
1.7.3.2	Application for Requesting an Overseas GMP Audit	m1-7-3-2-gmp-oap
1.7.A	Additional GMP Documents	m1-7-a-additional-gmp

Table 19 Heading Elements 1.8 – Information Relating to Pharmacovigilance

Section ID	Title	XML-Element
1.8	**Information Relating to Pharmacovigilance**	**m1-8-info-relating-to-pv**
1.8.1	Singapore-Specific Annex	m1-8-1-ssa
1.8.2	Reference RMP	m1-8-2-ref-rmp
1.8.3	Educational/RMP Materials	m1-8-3-edu-rmp-materials

1.8.3.1	Clean Proposed - Educational/RMP Materials	m1-8-3-1-edu-rmp-mat-clean
1.8.3.2	Annotated - Educational/RMP Materials	m1-8-3-2-edu-rmp-mat-annotated
1.8.3.3	Finalised Artwork - Educational/RMP Materials	m1-8-3-3-edu-rmp-mat-finalised

Please note that **PBRER, PSUR and RMP Reports** should be provided in **5.3.6** using node extensions with titles that begin with either “PBRER”, “PSUR” or “RMP Report” followed by the report description and/or a date period. Please see 3.6. Submission of PBRER/PSUR and RMP Reports and 4.4.3. Node Extensions.

Table 20 Heading Elements 1.9 – Foreign Regulatory Information

Section ID	Title	XML-Element
1.9	**Foreign Regulatory Information**	**m1-9-foreign-reg-info**
1.9.1	Registration Status in Other Countries	m1-9-1-status
1.9.2	Proof of Approval	m1-9-2-proof-approval
1.9.2.1	Proof of Approval from Reference Countries	m1-9-2-1-proof-approval-ref
1.9.2.2	Proof of Approval from Other Countries	m1-9-2-2-proof-approval-other
1.9.3	Data Set Similarities and Differences	m1-9-3-data-set-similarities
1.9.4	Foreign Evaluation/Assessment Reports	m1-9-4-foreign-evaluation-reports
1.9.5	Appendix 18A Dossier Clarification Supplement	m1-9-5-18a
1.9.6	Declaration on Rejection, Withdrawal and Deferral	m1-9-6-decl-rej-wd-def

Table 21 Heading Elements 1.A – Additional Data

Section ID	Title	XML-Element
1.A	**Additional Data**	**m1-a-additional-data**
1.A.1	[DESCRIPTION]	m1-a-1-additional-data

4.4.2. Leaf Element

The `leaf` elements provide the content for each heading element.

These elements contain the `title` element along with several other attributes, all based upon the ICH eCTD definition provided in the Electronic Common Technical Document Specification (Version 3.2.2).

Note that the structure and information associated with a Leaf should be created automatically by the eCTD software.

```
<m3-2-s-1-2-structure>
<leaf
   ID="Nba62a4e215fb40479b4151fa38bd80ad"
   operation="replace"
   xlink:href="m3/32-body-data/32s-drug-sub/olive-abc/32s1-gen-info/structure.pdf"
   checksum="14f0984f1116ac9d4fe43d31c7fee14f"
   checksum-type="MD5"
   modified-file="../0001/index.xml#Nba62a4e215fb40479b4151fa38bd80ad">
   <title>3.2.S.1.2 Structure</title>
</leaf>
</m3-2-s-1-2-structure>
```

Footnote: The line breaks in the above example have been created here to make the display of the attributes more user friendly but will likely not be present in the actual XML file.

Figure 31 Leaf Element Explained

Each `Leaf` element contains the following attributes when appropriate:

- **ID** – The ID attribute is intended to be a unique reference within the Submission that can be used to reference the item from another item within the XML document.
- **Operation** – Indicates the action being performed e.g., New, Replace, Delete or Append
- **xlink:href** – Provides the reference (path) to the actual content file. Must be relative to the Application Folder.
- **Checksum** – The checksum value for the file being submitted. A checksum is a sequence of numbers and letters used to check data for validity. If we know the checksum of the original file, we can use a checksum utility to confirm the copy received and evaluated is identical.
- **Checksum Type** – The checksum algorithm used. The checksum-type can be indicated in upper or lower case (checksum-type="md5" or checksum-type="MD5"). You can repeat the optional node extension and Leaf elements as required. The schema will ensure the checksum-type attribute contains either "MD5" or "md5".
- **Modified File** – Provides the location of the `Leaf` that is being modified (i.e., replaced, appended or deleted) by the `Leaf` element. The modified-file attribute points to the "index.xml" file and the Leaf ID of the Leaf being altered.

- **Title** – A practical name for the file being referenced by the Leaf. This is the only thing the evaluator will see and should be descriptive and distinguishing, especially in sections where multiple `Leaf` elements are being submitted.

Operation – Append should only be used in connection with Study Tagging Files.

4.4.3. Node Extensions

Node extensions are additional heading structures beyond those defined by the Specifications, generally equated to an additional subfolder in a defined section and are a way of providing additional information in the Sequence.

The node extension should be visualised as an extra heading in the CTD structure and should be displayed when viewing the XML backbone.

Node extensions should not be changed during the life cycle once established. Note that changes in the Titles associated with the node extensions would constitute a change and must be avoided to prevent validation issues.

General Rules for Using Node Extensions:

- Only use node extensions at the lowest level of the eCTD structure.

  Example: you can use a node extension at the level 5.3.5.1 but not at the level 5.3

- Use node extensions to group documents made up of multiple Leaf elements.

  Example: a clinical study made up of separate files for the synopsis, main body and individual appendices should be grouped together under a node extension with the Study Identifier as its Title attribute.

- Nest the node extensions but make sure the first node extension is at the lowest level in the eCTD structure. Nested node extensions are not allowed in Module 1.

  Example: a node extension may be added in Module 5.3.7 to group together files with the Study Identifier as Title attribute. Further node extensions may be added as children of the Study Identifier node, separating Case Report Forms (CRFs), if submitted, from individual patient listings.

- Make `title` elements short, precise, and informative. Do not repeat information already categorised by heading elements.

- Place the most important identifying/distinguishing information at the beginning so we do not have to scroll to the end of the title.

You can use the `node-extension` elements:

- to define structures beyond the Heading Elements

- wherever a leaf element is allowed in the schema

- to organise multiple files which are needed under a normal eCTD heading

  Example: nonclinical studies with multiple files provided in 4.2

  Example: complex presentation of data in the analytical procedures and validation of analytical procedures sections of 3.2.S.4.2/3 and 3.2.P.5.2/3

You should use the `node-extension` elements:

- for all clinical studies and content provided in Module 5.3

Note that if node extensions are not used for clinical studies, a warning will result in the validation.

Do not use the `node-extension` elements:

- if ICH-specified subheadings already exist

  Example: do not use the following as node extensions:

  – *indication*
  – *excipient*
  – *manufacturer*
  – *drug substance*
  – *drug product.*

- if they are not for the lowest level of the eCTD Structure

Note that using node extensions where ICH subheadings already exist or at a level that is not the lowest level will result in a warning in the validation.

The node-extension structure complies with general ICH eCTD specifications, but it is not a blanket permission to use the structures anywhere or without consideration. You may contact HSA for advice if the usage is novel.

The optional `node-extension` element contains a single mandatory `title` element, followed by at least one `Leaf` element, and can be followed by another optional `node-extension` element.

```
<m1-a-additional-data>
 <m1-a-1-additional-data>
  <node-extension>
   <title>1.A.1 Node Extension</title>
   <leaf ID="N1A11" operation="new"
     xlink:href=
     "1-a-additional-data/1-a-1-additional-data/1-a-1-additional-data-1.pdf"
```

```
      checksum="a9b5c26f2621ad01cdb72683e6b887f9" checksum-type="MD5">
         <title>1.A.1.1 Additional Data</title>
   </leaf>
   <leaf ID="N1A12" operation="new"
     xlink:href=
     "1-a-additional-data/1-a-1-additional-data/1-a-1-additional-data-2.pdf"
     checksum="33d0520400df59144bdd573d44021d3f" checksum-type="MD5">
         <title>1.A.1.2 Additional Data</title>
   </leaf>
   <leaf ID="N1A13" operation="new"
     xlink:href=
     "1-a-additional-data/1-a-1-additional-data/1-a-1-additional-data-3.pdf"
     checksum="ed2caa23a1d282b846bd20755286bf36" checksum-type="MD5">
         <title>1.A.1.3 Additional Data</title>
   </leaf>
  </node-extension>
 </m1-a-1-additional-data>
</m1-a-additional-data>
```

Figure 32 Node Extension Explained

4.4.4. Regional Information 2.3.R / 3.2.R

The general structure of the Regional Information is as follows:

R Regional Information

R.1 Checklist for Human Blood Product

R.2 TSE Checklist

R.3 Product Interchangeability

R.4 Blank Production Batch Record

R.A Additional Regional Information

All fields are optional and only submitted where applicable.

4.4.4.1. 2.3.R Regional Information Summary

A single document should be provided summarising the content provided in 3.2.R. The document can include a TOC of all the content provided in 3.2.R followed by a summary of any particulars that need to be highlighted.

4.4.4.2. 3.2.R Regional Information

Leaf elements in 3.2.R Regional Information heading should be provided using node extensions. PDF files should not be included as leaf elements directly under the 3.2.R Regional Information heading. Acceptable titles of the node extensions are as listed above. Structure numbers should be included in the titles and should be complete, e.g., 3.2.R.1 Checklist for Human Blood Product.

Any Additional Regional Information required or requested by HSA should be provided as leaves in the 3.2.R.A Additional Regional Information node extension. Each document should be provided separately and should have a Leaf Title clearly identifying the content.

A Warning will be reported if the naming convention of the title is not followed.

Later in life cycle management of the regional files, the exact naming convention of the titles of node extensions must be used when the node extension(s) was (were) created for the first time under the heading.

4.5. Life Cycle Operations

The following four life cycle operations are defined under the ICH eCTD specification:

- New
- Replace
- Delete
- Append

We encourage you to:

- Use New, Replace, and Delete.
- Only use Append as part of the Study Tagging Files (STF) as defined by the ICH eCTD Backbone File Specification for Study Tagging Files. If you use Append for any other purpose, you will receive a validation error.

Note that any unauthorised use of Append will result in a rejection of the Sequence.

4.5.1. Specific Life Cycle Operations for Singapore

The nodes with specific life cycle operations mandated for a Singapore eCTD are summarised in Table 22 Nodes with Specific Life Cycle Operations. Adherence to these specific requirements will be validated.

Table 22 Nodes with Specific Life Cycle Operations

Section ID	Business Terminology	Life Cycle Operation	Validation Severity
1.0	**Correspondence**		
1.0.1	Cover letter	New	Error
1.0.2	Note to Evaluator	New	Error

Section ID	Business Terminology	Life Cycle Operation	Validation Severity
1.2	**Administrative Information**		
1.2.2**	Checklists	New	Error
1.2.4	Table of Summary of Changes	New	Warning
1.3	**Product Information**		
1.3.1**	Outer Carton Labels (OCL)	Replace*	Warning
1.3.2**	Inner/Blister Labels (IBL)	Replace*	Warning
1.3.3**	Package Insert (PI)	Replace*	Warning
1.3.4**	Patient Information Leaflet (PIL)	Replace*	Warning
1.3.5**	Approved Foreign Labelling (SPC/PI/PIL)	Replace*	Warning
1.8	**Information Relating to Pharmacovigilance**		
1.8.1	Singapore-Specific Annex	Replace*	Warning
1.8.2	Reference RMP	Replace*	Warning
1.8.3**	Educational/RMP materials	Replace*	Warning

* The first time we receive a document in these sections the operation should be 'New'. Once a document has been provided, the content should only be replaced in all future Sequences. If 'New' content is provided, this will create a Warning in some cases to allow for the rare occasion when 'New' content should be provided e.g., content for additional countries/regions.

** Applies to all Subnodes with content e.g., Approved, Clean Proposed, Annotated, Finalised Artwork, etc.

Proposed Product Information for New Applications should be placed in the Clean Proposed section. If amendments are required prior to registration, an annotated copy of the proposal should be placed in the Annotated section and a clean copy should be provided in the Clean Proposed section which replaces the previous version. Once the Product Information in the Clean Proposed section has been approved, the PDF version should be submitted in the Approved section in a `Closing Information` Sequence via cross-referencing. The physical file should not be provided again.

When there are proposed changes in subsequent Submissions to the Product Information, the clean amended file(s) should be submitted in the Clean Proposed section and an annotated copy of the proposals should be placed in the Annotated section. Once Proposed changes presented in Clean Proposed have been approved, a `Closing Information` Sequence should be provided that replaces the content (PDF version only) in the Approved section with that in the Clean Proposed section by cross-referencing to the content provided in the earlier sequence under Clean Proposed. The physical file should not be provided again.

Please see 3.8. Reusing Files for more information on reusing content already submitted.

4.5.2. Life Cycle Operations for a Submission Withdrawal

Submission Withdrawal:

When withdrawing a Submission that is still under evaluation, the following attributes should be applied in the Envelope element:

- The Submission Type should be consistent with the Type set in the Related Sequence.
- The Sequence Type should be set to “Submission Withdrawal”.
- The Sequence Description should be set to “Withdrawal of…” and indicate the detail of the Submission that was indicated in the Description of the Related Sequence.
- Submission Withdrawal is a new Sequence in the Submission that is still under evaluation, so the Related Sequence should be set to the “Initial” Sequence of the Submission.
- The Cover Letter should be the only document submitted as New.
- If Work Grouping was done in the first Sequence, see 4.5.2.1. Submission Withdrawals and Work Grouping on how to address the reactivation of those activities.

When the Sequence Type is set to Withdrawal, the validation rules ensuring that documents for the Submission Type are included are suspended.

4.5.2.1. Submission Withdrawals and Work Grouping

In Work Grouping, the results of each Submission evaluation should be the same. If Work Grouping was done and Submission Withdrawal is performed, all Submissions combined in the Initial Sequence of the Submission will be withdrawn.

If only parts of the Submissions included in the Initial Sequence are approved, the approved Submissions will have to be extracted out of the Submission group of the withdrawn Submission. In the Submission Withdrawal Sequence, the content related to the Submissions not being withdrawn should not be replaced or deleted. Instead, and in addition to the Submission Withdrawal Sequence, a new Sequence should be submitted as a New Initial Submission in which all current content from the Submissions not being withdrawn is referenced again using the Replace operation. The documents should not be provided again, but only referenced using content reuse. For more information on content reuse, please see 3.8 Reusing Files.

4.5.3. Life Cycle Operations for Rejected Submissions

If a Submission was submitted on its own without Work Grouping, no further action is required if a Submission is rejected. A Submission evaluation tool should be able to display content excluding the content and changes introduced in rejected Submissions.

4.5.3.1. Rejected Submissions and Work Grouping

If Work Grouping was done and one of the Submissions is rejected, all Submissions combined in the Initial Sequence will be rejected.

An additional Sequence should be submitted as an Initial Sequence in a new Submission in which all current content from the Submissions not rejected is referenced again using the Replace operation. The documents should NOT be provided again, only referenced again using content reuse. For more information on content reuse, please see 3.88 Reusing Files.

4.6. Files and Folders

4.6.1. File and Folder Naming Conventions

Naming conventions for the content files are not part of the Validation Criteria.

You may use files submitted in other regions without re-naming, but:

- Ensure all content is referenced by the appropriate XML files for efficient navigation.
- Provide precise but informative Leaf Titles to aid evaluators.
- Ensure the basic construction of the eCTD is maintained.
- Adhere to the basic ICH eCTD rules for folder and file names:
  - Use alphanumeric lower-case characters only – for example a-z & 0-9.
  - Do not use spaces.
  - Do not use any special characters other than hyphen “-“.
- Adhere to the naming conventions for leaf titles as described in Table 23 Minimum Naming Conventions Matrix.
- Avoid ending file names with “.p” as this would result in rejection during validation, e.g., “3.2.p.pdf”.

If a file naming convention is sought for technical purposes, the elements defined for each of the leaf elements e.g., “m1-0-1-cover-letter” could be used as a file name and the structure number could be used to create folders e.g., “1-0-1”. This is not required but could be used as a best practice recommendation where necessary.

Only the Sequence(s) being submitted should be included in the Application Folder submitted. The first 2 levels in the folder structure within an Application Folder are <SG ECTD ID>/<SEQUENCE NUMBER>.

Table 23 Minimum Naming Conventions Matrix

Folders	Files	Description
e20220920sg0001		Application folder named after SG eCTD ID
0001		Sequence folder with four-digit number e.g., 0001
m1		Content folder for Module 1 documents in accordance with ICH
sg		Singapore country specific folder
	sg-regional.xml	Singapore regional index file for Module 1
m2		Content folder for Module 2 documents in accordance with ICH
m3		Content folder for Module 3 documents in accordance with ICH
m4		Content folder for Module 4 documents in accordance with ICH
m5		Content folder for Module 5 documents in accordance with ICH
util		Util folder in accordance with ICH
dtd		DTD and Schema[3] folder in accordance with ICH
	sg-regional.xsd	Singapore regional backbone schema for Module 1
	xlink.xsd	W3C schema for Xlink 1.1 (referenced from sg-regional.xsd)
	xml.xsd	W3C schema for XML namespace (referenced from sg-regional.xsd)
	ich-ectd-3-2.dtd	ICH DTD for Modules 2 to 5
style		Stylesheet folder in accordance with ICH
	ectd-2-0.xsl	ICH stylesheet for Modules 2 to 5
	sg-regional.xsl	Regional stylesheet for Module 1
index.xml		Index file in accordance with ICH
index-md5.txt		MD5 checksum in accordance with ICH

If folders/files recommendations are desired, the section number could be used for folder names and xml elements defined could be used as file name core components with a variable appended.

[3] Document Type Definition (DTD) - A document type definition is a set of markup declarations that define the document structure with a list of validated elements and attributes, the valid building blocks of an XML document. An XML schema (schema) is similar to a DTD, but also allows for the definition of datatypes for elements and attributes and allows support for namespaces, whereas a DTD does not.

4.6.2. Folder and File Name – Path Length

Ensure the overall length of the folder and file name path (counting starts with the first character of the Application Folder) does not exceed 180 characters, for any file in any module.

4.6.3. File Size

File size limit is part of the Validation Criteria. The size limit is 50GB for the zip file and 500MB for individual files.

4.6.4. Source Documents

Source Documents (Microsoft® Word .docx/.doc or Rich Text Format (.rtf)) should be submitted along with PDF files in the appropriate Module 1 sections using the life cycle operation New, Replace or Delete. Hyperlinks should be placed in PDFs but no hyperlinks are required in any of the Word Files.

Table 24 Source File Requirements

Requirement	Requirement Details
1.2.2 Checklists	MS Word Only
1.3.3.2 Clean Proposed - Package Insert (PI)	MS Word File in addition to the PDF
1.3.3.3 Annotated - Package Insert (PI)	MS Word File in addition to the PDF
1.3.4.2 Clean Proposed - Patient Information Leaflet (PIL)	MS Word File in addition to the PDF
1.3.4.3 Annotated – Patient Information Leaflet (PIL)	MS Word File in addition to the PDF
1.8.3.1 Clean Proposed - Educational/RMP Materials	MS Word File in addition to the PDF
1.8.3.2 Annotated – Educational/RMP Materials	MS Word File in addition to the PDF

5. eCTD Preparation Tools

5.1. General Information about Solutions

HSA does not mandate, endorse or recommend any software to prepare an eCTD Submission. eCTD is an international standard and any solution capable of producing a valid SG eCTD will be able to provide an Application compatible with any solution the Singapore Authority has chosen to use for evaluation.

It is important to note that the evaluation tool used by an Authority should in no way influence the solution selected by an Applicant. Any eCTD created by any eCTD Tool that conforms to Singapore requirements will work with any eCTD evaluation solution that also conforms to the Singapore requirements. Please be wary of solution providers that would argue differently.

We recommend you, as the Applicant to:

- Prepare the eCTD using an authenticated commercial eCTD preparation tool.

  There is a wide variety of options available, both in terms of multiple vendors and of approaches – for example:

  – Installed Software

  – Software as a Service

  – Service Providers

- Find a solution which supports current Singapore eCTD requirements and meets your overall business needs.
- Validate the prepared Sequences using an authenticated commercial eCTD validation tool.

eCTD validation tools are not just XML checkers or parsers. The validation tools evaluate the technical content of the Sequence for the eCTD Application. We recommend you use a validation tool that:

- supports checking current Singapore eCTD requirements.
- minimises the possibility of technical validation errors which can cause delays in the overall regulatory process.

6. Appendix A: Best Practice Leaf Title Recommendations

Shaded sections are eCTD elements where Leaf elements should not be added. No documents should be created at that granularity. These are only listed here for organisational purposes.

Some titles include values in brackets – for example [DESCRIPTION]. These variables should be replaced with the item indicated in brackets.

Dashes are the hyphens character, "-", not the en dash.

Companies are encouraged to develop internal policies on naming conventions. The following is provided as best practice recommendations but can be varied as needed by internal policies as long as the Leaf titles are descriptive and distinctive. Leaf titles should be precise, distinguishing, and as short as possible.

Table 25 Best Practice Leaf Title Recommendations

Section	Best Practice Leaf Title
1.0	**Correspondence**
1.0.1	[SEQUENCE] Cover Letter [DESCRIPTION]
1.0.2	[SEQUENCE] Note to Evaluator
1.0.3	Correspondence [DATE] [DESCRIPTION]
1.0.4	Response [DATE OF CORRESPONDENCE FROM HSA] [DESCRIPTION]
1.0.5	Meeting Information [DESCRIPTION]
1.2	**Administrative Information**
1.2.1	[SEQUENCE] App Form [PRODUCT] [STRENGTH] [DESCRIPTION]
1.2.2	**Checklists**
1.2.2.1	[SEQUENCE] Appendix 2a Checklist [DESCRIPTION]
1.2.2.2	[SEQUENCE] Appendix 2b Checklist [DESCRIPTION]
1.2.2.3	[SEQUENCE] Appendix 13a/14a Checklist [DESCRIPTION]
1.2.2.4	[SEQUENCE] Appendix 13b/14b Checklist [DESCRIPTION]
1.2.2.5	[SEQUENCE] Appendix 13c/14c Checklist [DESCRIPTION]
1.2.3	**Annexes**
1.2.3.1	Letter of Authorisation [DESCRIPTION]
1.2.3.2	**Change in Applicant**
1.2.3.2.1	Letter of Authorisation to New Registrant [DESCRIPTION]
1.2.3.2.2	Written Confirmation of Hand-over of Dossier
1.2.3.2	Change in Applicant [NEW APPLICANT]
1.2.3.3	Declaration for [NDA/GDA] Verification or Declaration for GDA Verification-CECA
1.2.3.4	**Patent Declaration**
1.2.3.4.1	Patent Declaration Form
1.2.3.4.2	Evidence of Authorisation [DESCRIPTION]
1.2.4	Table of Summary of Changes
1.2.A	Additional Administrative Information [DESCRIPTION]
1.3	**Product Information**
1.3.1	**Outer Carton Labels (OCL)**

Section	Best Practice Leaf Title
1.3.1.1	Approved - OCL - [PACK SIZE] [FORMAT] [DATE APPROVED]
1.3.1.2	Clean Proposed - OCL - [PACK SIZE] [FORMAT] [DATE PROPOSED]
1.3.1.3	Annotated - OCL - [PACK SIZE] [FORMAT] [DATE PROPOSED]
1.3.2	**Inner/Blister Labels (IBL)**
1.3.2.1	Approved - IBL - [FORMAT] [DATE PROPOSED]
1.3.2.2	Clean Proposed - IBL - [FORMAT] [DATE PROPOSED]
1.3.2.3	Annotated - IBL - [FORMAT] [DATE PROPOSED]
1.3.3	**Package Insert (PI)**
1.3.3.1	Approved - PI - [FORMAT] [DATE PROPOSED]
1.3.3.2	Clean Proposed - PI - [FORMAT] [DATE PROPOSED]
1.3.3.3	Annotated - PI - [FORMAT] [DATE PROPOSED]
1.3.4	**Patient Information Leaflet (PIL)**
1.3.4.1	Approved - PIL - [FORMAT] [DATE PROPOSED]
1.3.4.2	Clean Proposed - PIL - [FORMAT] [DATE PROPOSED]
1.3.4.3	Annotated - PIL - [FORMAT] [DATE PROPOSED]
1.3.5	**Approved Foreign Labelling (SPC/PI/PIL)**
1.3.5.1	[COUNTRY] - Reference Agency Labelling [PI TYPE]
1.3.5.2	[COUNTRY] - Proof of Approval Agency [PI TYPE]
1.3.5.3	[COUNTRY] - Other Agency [PI TYPE]
1.3.6	**Declarations on Foreign Text/Braille**
1.4	**Information about the Experts**
1.4.1	Info about the Experts - Quality
1.4.2	Info about the Experts - Nonclinical
1.4.3	Info about the Experts - Clinical
1.5	**Master Files and Certificates of Suitability**
1.5.1	DMF Acknowledgement Email [DMF NUMBER]
1.5.2	**Letter of Access**
1.5.2.1	DMF Letter of Access [SUBSTANCE] [DMF NUMBER] [DMF HOLDER/COMPANY]
1.5.2.2	PMF Letter of Access [PMF NUMBER] [PMF HOLDER/COMPANY]
1.5.3	EMA PMF [PMF HOLDER]
1.5.4	CEP [SUBSTANCE] [CERTIFICATE HOLDER]
1.6	**Environmental Risk Assessment**
1.6.1	Non-GMO
1.6.2	GMO
1.7	**Good Manufacturing Practice**
1.7.1	**GMP Certificates or Proof of GMP Compliance**
1.7.1.1	Drug Substance GMP Certificate [SUBSTANCE] [MANUFACTURER]
1.7.1.2	FPP GMP Certificate [MANUFACTURER] [DOSAGE]
1.7.1.3	Batch Releaser GMP Certificate [SUBSTANCE] [MANUFACTURER] [DOSAGE]
1.7.2	Description of the Batch Numbering System
1.7.3	**HSA GMP Conformity Assessment Application**

Section	Best Practice Leaf Title
1.7.3.1	Application for GMP Evidence Evaluation [DESCRIPTION]
1.7.3.2	Application for Requesting an Overseas GMP Audit [DESCRIPTION]
1.7.A	Additional GMP Document [DESCRIPTION]
1.8	**Information Relating to Pharmacovigilance**
1.8.1	Singapore-Specific Annex [DATE]
1.8.2	Reference RMP [COUNTRY-VERSION-DATE]
1.8.3	**Educational/RMP Materials**
1.8.3.1	Clean Proposed - Educational/RMP Materials [DESCRIPTION] [DATE PROPOSED]
1.8.3.2	Annotated - Educational/RMP Materials [DESCRIPTION] [DATE PROPOSED]
1.8.3.3	Finalised Artwork - Educational/RMP Materials [DESCRIPTION]
1.9	**Foreign Regulatory Information**
1.9.1	Registration Status in Other Countries
1.9.2	**Proof of Approval**
1.9.2.1	Proof of Approval Reference Country [COUNTRY]
1.9.2.2	Proof of Approval Other Country [COUNTRY]
1.9.3	Data Set Similarities and Differences
1.9.4	Foreign Evaluation Reports [COUNTRY] [DATE]
1.9.5	Appendix 18A Dossier Clarification Supplement
1.9.6	Declaration on Rejection/Withdrawal/Deferral
1.A	**Additional Data***
1.A.1	[DESCRIPTION]
2	**Summaries and Overviews**
2.2	Introduction
2.3.S	Drug Substance [SUBSTANCE] [MANUFACTURER]
2.3.P	Drug Product [MANUFACTURER] [DOSAGE]
2.3.A	Appendices
2.3.R	Regional Information
2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	**Nonclinical Written and Tabulated Summaries**
2.6.1	Introduction
2.6.2	Pharmacology Written Summary
2.6.3	Pharmacology Tabulated Summary
2.6.4	Pharmacokinetics Written Summary
2.6.5	Pharmacokinetics Tabulated Summary
2.6.6	Toxicology Written Summary
2.6.7	Toxicology Tabulated Summary
2.7	**Clinical Summary**
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods
2.7.2	Summary of Clinical Pharmacology Studies
2.7.3	Summary of Clinical Efficacy

Section	Best Practice Leaf Title
2.7.4	Summary of Clinical Safety
2.7.5	Literature References
2.7.6	Synopses of Individual Studies
3	**Quality**
3.2	**Body of Data**
3.2.S	**Drug Substance**
3.2.S.1	**General Information**
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	**Manufacturer**
3.2.S.2.1	Manufacturer
3.2.S.2.2	Description of Manufacturing Process and Process Controls
3.2.S.2.3	Control of Materials
3.2.S.2.4	Controls of Critical Steps and Intermediates
3.2.S.2.5	Process Validation and/or Evaluation
3.2.S.2.6	Manufacturing Process Development
3.2.S.3	**Characterisation**
3.2.S.3.1	Elucidation of Structure and Other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	**Control of Drug Substance**
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures [DESCRIPTION]*
3.2.S.4.3	Validation of Analytical Procedures [DESCRIPTION]*
3.2.S.4.4	Batch Analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference Standards or Materials [DESCRIPTION]
3.2.S.6	Container Closure System
3.2.S.7	**Stability**
3.2.S.7.1	Stability Summary and Conclusions
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3	Stability Data
3.2.P	**Drug Product**
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.3.1	Manufacturer [MANUFACTURER]
3.2.P.3.2	Batch Formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls
3.2.P.3.4	Controls of Critical Steps and Intermediates
3.2.P.3.5	Process Validation and/or Evaluation
3.2.P.4	**Control of Excipients**
3.2.P.4.1	Compendial Excipients
3.2.P.4.1	Specifications

Section	Best Practice Leaf Title
3.2.P.4.2	Analytical Procedures
3.2.P.4.3	Validation of Analytical Procedures
3.2.P.4.4	Justification of Specifications
3.2.P.4.5	Excipients of Human or Animal Origin
3.2.P.4.6	Novel Excipients
3.2.P.5	**Control of Drug Product**
3.2.P.5.1	**Specification**
3.2.P.5.2	Analytical Procedures [DESCRIPTION]*
3.2.P.5.3	Validation of Analytical Procedures [DESCRIPTION]*
3.2.P.5.4	Batch Analyses
3.2.P.5.5	Characterisation of Impurities
3.2.P.5.6	Justification of Specifications
3.2.P.6	Reference Standards or Materials [DESCRIPTION]
3.2.P.7	Container Closure System
3.2.P.8	**Stability**
3.2.P.8.1	Stability Summary and Conclusion
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment
3.2.P.8.3	Stability Data
3.2.A	**Appendices**
3.2.A.1	Facilities and Equipment [MANUFACTURER] [SUBSTANCE if applicable]
3.2.A.2	Adventitious Agents Safety Evaluation [MANUFACTURER] [SUBSTANCE if applicable]
3.2.A.3	Excipients [EXCIPIENT]*
3.2.R	**Regional Information**
3.2.R.1	Checklist for Human Blood Product [DESCRIPTION]
3.2.R.2	TSE Checklist [DESCRIPTION]
3.2.R.3	Product Interchangeability [DESCRIPTION]
3.2.R.4	Blank Production Batch Record [DESCRIPTION]
3.2.R.A	Additional Regional Information
3.3	[AUTHORS(S), DATE] e.g., Smith-2018
4	**Nonclinical Study Reports****
4.2	**Study Reports**
4.2.1	**Pharmacology**
4.2.1.1	[STUDY ID] [DESCRIPTION]
4.2.1.2	[STUDY ID] [DESCRIPTION]
4.2.1.3	[STUDY ID] [DESCRIPTION]
4.2.1.4	[STUDY ID] [DESCRIPTION]
4.2.2	**Pharmacokinetics**
4.2.2.1	[STUDY ID] [DESCRIPTION]
4.2.2.2	[STUDY ID] [DESCRIPTION]
4.2.2.3	[STUDY ID] [DESCRIPTION]
4.2.2.4	[STUDY ID] [DESCRIPTION]
4.2.2.5	[STUDY ID] [DESCRIPTION]
4.2.2.6	[STUDY ID] [DESCRIPTION]

Section	Best Practice Leaf Title
4.2.2.7	[STUDY ID] [DESCRIPTION]
4.2.3	**Toxicology**
4.2.3.1	[STUDY ID] [SPECIES] [ROUTE OF ADMIN] [DESCRIPTION]
4.2.3.2	[STUDY ID] [SPECIES] [ROUTE OF ADMIN] [DURATION] [DESCRIPTION]
4.2.3.3	**Genotoxicity**
4.2.3.3.1	[STUDY ID] [DESCRIPTION]
4.2.3.3.2	[STUDY ID] [DESCRIPTION]
4.2.3.4	**Carcinogenicity**
4.2.3.4.1	[STUDY ID] [SPECIES] [DESCRIPTION]
4.2.3.4.2	[STUDY ID] [DESCRIPTION]
4.2.3.4.3	[STUDY ID] [DESCRIPTION]
4.2.3.5	**Reproductive and Developmental Toxicity**
4.2.3.5.1	[STUDY ID] [DESCRIPTION]
4.2.3.5.2	[STUDY ID] [DESCRIPTION]
4.2.3.5.3	[STUDY ID] [DESCRIPTION]
4.2.3.5.4	[STUDY ID] [DESCRIPTION]
4.2.3.6	[STUDY ID] [DESCRIPTION]
4.2.3.7	**Other Toxicity Studies**
4.2.3.7.1	[STUDY ID] [DESCRIPTION]
4.2.3.7.2	[STUDY ID] [DESCRIPTION]
4.2.3.7.3	[STUDY ID] [DESCRIPTION]
4.2.3.7.4	[STUDY ID] [DESCRIPTION]
4.2.3.7.5	[STUDY ID] [DESCRIPTION]
4.2.3.7.6	[STUDY ID] [DESCRIPTION]
4.2.3.7.7	[STUDY ID] [DESCRIPTION]
4.3	[AUTHORS(S), DATE] e.g., Smith-2018
5	**Clinical Study Reports****
5.2	Tabular Listing of all Clinical Studies
5.3	**Clinical Study Reports**
5.3.1	**Reports of Biopharmaceutic Studies**
5.3.1.1	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.1.2	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.1.3	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.1.4	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.2	**Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials**
5.3.2.1	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.2.2	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.2.3	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.3	**Reports of Human Pharmacokinetic (PK) Studies**
5.3.3.1	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.3.2	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.3.3	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.3.4	[STUDY ID] [E3 SECTION] [DESCRIPTION]

Section	Best Practice Leaf Title
5.3.3.5	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.4	**Reports of Human Pharmacodynamic (PD) Studies**
5.3.4.1	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.4.2	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.5	**Reports of Efficacy and Safety Studies**
5.3.5.1	[STUDY ID] [TYPE OF CONTROL] [E3 SECTION] [DESCRIPTION]
5.3.5.2	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.5.3	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.5.4	[STUDY ID] [E3 SECTION] [DESCRIPTION]
5.3.6	[PBRER] [DESCRIPTION] [DATE/DATA LOCK PERIOD]; or [PSUR] [DESCRIPTION] [DATE/DATA LOCK PERIOD]; or [RMP Report] [DESCRIPTION] [DATE/DATA LOCK PERIOD]
5.3.7	[STUDY ID] [DESCRIPTION]
5.4	[AUTHORS(S), DATE] e.g., Smith-2018

*Multiple leaves or node extensions may be provided under these headings. Refer to ICH eCTD Specification.

**For study reports in Module 4 and Module 5, the suggested titles are for node extension, instead of leaf titles.

7. Appendix B: Singapore eCTD Granularity Annex

The following granularity should be observed when submitting the regional content to the SG-HSA.

Content not Allowed	A comprehensive file is not allowed at this level
ONE File	One comprehensive file should be provided for these sections
MULTIPLE Files	One or more files can be provided if appropriate

Module 1 SG	1.0	1.0.1		
		1.0.2		
		1.0.3		
		1.0.4		
		1.0.5		
	1.2	1.2.1		
		1.2.2	1.2.2.1	
			1.2.2.2	
			1.2.2.3	
			1.2.2.4	
			1.2.2.5	
		1.2.3	1.2.3.1	
			1.2.3.2	1.2.3.2.1
				1.2.3.2.2
			1.2.3.3	
			1.2.3.4	1.2.3.4.1
				1.2.3.4.2
		1.2.4		
		1.2.A		
	1.3	1.3.1	1.3.1.1	
			1.3.1.2	
			1.3.1.3	
		1.3.2	1.3.2.1	
			1.3.2.2	
			1.3.2.3	

		1.3.3	1.3.3.1
			1.3.3.2
			1.3.3.3
		1.3.4	1.3.4.1
			1.3.4.2
			1.3.4.3
		1.3.5	1.3.5.1
			1.3.5.2
			1.3.5.3
		1.3.6	
	1.4	1.4.1	
		1.4.2	
		1.4.3	
	1.5	1.5.1	
		1.5.2	1.5.2.1
			1.5.2.2
		1.5.3	
		1.5.4	
	1.6	1.6.1	
		1.6.2	
	1.7	1.7.1	1.7.1.1
			1.7.1.2
			1.7.1.3
		1.7.2	
		1.7.3	1.7.3.1
			1.7.3.2
		1.7.A	
	1.8	1.8.1	
		1.8.2	
		1.8.3	1.8.3.1
			1.8.3.2
			1.8.3.3

	1.9	1.9.1	
		1.9.2	1.9.2.1
			1.9.2.2
		1.9.3	
		1.9.4	
		1.9.5	
		1.9.6	
	1.A	1.A.1	
Module 3	3.2	3.2.R	3.2.R.1
			3.2.R.2
			3.2.R.3
			3.2.R.4
			3.2.R.A

8. Change Control

Factors that could affect the content of the specification include, but are not limited to:

- Changes in the Content of the Module 1 for the CTD
- Update of Standards that are already in use within the eCTD
- New Standards for Creating and/or Using eCTD
- New Functional Requirements
- Experience with Using eCTD, in particular Module 1

In general, a transition time of at least 6 months will be provided for the implementation of changes in the Specification.

If you have any feedback, comments, or questions, please visit HSA | Electronic Common Technical Document (ECTD) Submissions.

9. Version History

Version	Description of Change	Author	Effective Date
0.9	Version for industry review	Singapore eCTD Project Team	N.A.
1.0	Initial version	Singapore eCTD Project Team	2024-09-25