

**SG-HSA eCTD Specification and Guidance for Use**

Module 1 and Regional Information

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# Introduction

We are releasing an initial version 0.9 for industry comment, however, all text within the specification is aimed at the official initial version 1.0 that will be used for the first eCTDs to be submitted. No Applications using the version 0.9 specifications will be accepted.

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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) and [Guidance on Therapeutic Products Registration in Singapore](https://www.hsa.gov.sg/therapeutic-products/guidance-documents).

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.

Version 1.0 of the Specifications should be read in combination with:

* [Guidance on Therapeutic Products Registration in Singapore](https://www.hsa.gov.sg/therapeutic-products/guidance-documents)
* the [SG-HSA eCTD Validation Criteria](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) version 1.0
* the [SG-HSA eCTD Q&A Document](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) version 1.0

The eCTD Specifications are designed to assist software vendors and technical staff with understanding the technical setup and creation of a Singapore eCTD. We encourage regulatory personnel to read and understand the Specifications 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](https://www.hsa.gov.sg/therapeutic-products/guidance-documents), sections 2, 4 and 6 of the [SG-HSA eCTD Validation Criteria](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) and information clarified in the [SG-HSA eCTD Q&A Document](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

**Comment about ICH eCTD version 4.0**

Internationally, the eCTD is currently implemented using the ICH eCTD Specifications version 3.2.2. The eCTD Specifications 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.

## 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 4.0. Hence, the terminology in the SG-HSA Specifications is mostly consistent with the proposed terminology in the ICH eCTD version 4.0 Specifications. 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 a registration filed under an Application-UUID. An Application is comprised of all Submissions and Sequences over time.  Application is a term consistent with the eCTD version 4.0 specifications 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. |
| Application-UUID | A universally unique identifier (UUID) as specified by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834-8:2005.  It is a 128-bit label and is unique for practical purposes when generated according to the standard methods.  A UUID can be created online using free Online UUID Generators.  The same UUID will be used for all Sequences of an eCTD Application and cannot ever be changed. |
| 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 in a non-eCTD format. No new content should be introduced in a Baseline Submission except for what is defined in the [Document Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions). |
| 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. They structure the content and data so that the Application can be managed and displayed over the entire life cycle of the product. |
| 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. |
| 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 but should not contain multiple pharmaceutical forms. An Application is made up of multiple Submissions.
* The Submission level represents a regulatory activity which may be made up of one or more sequences depending on whether additional information or changes are required after the initial sequences of each Submission has been reviewed. 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.

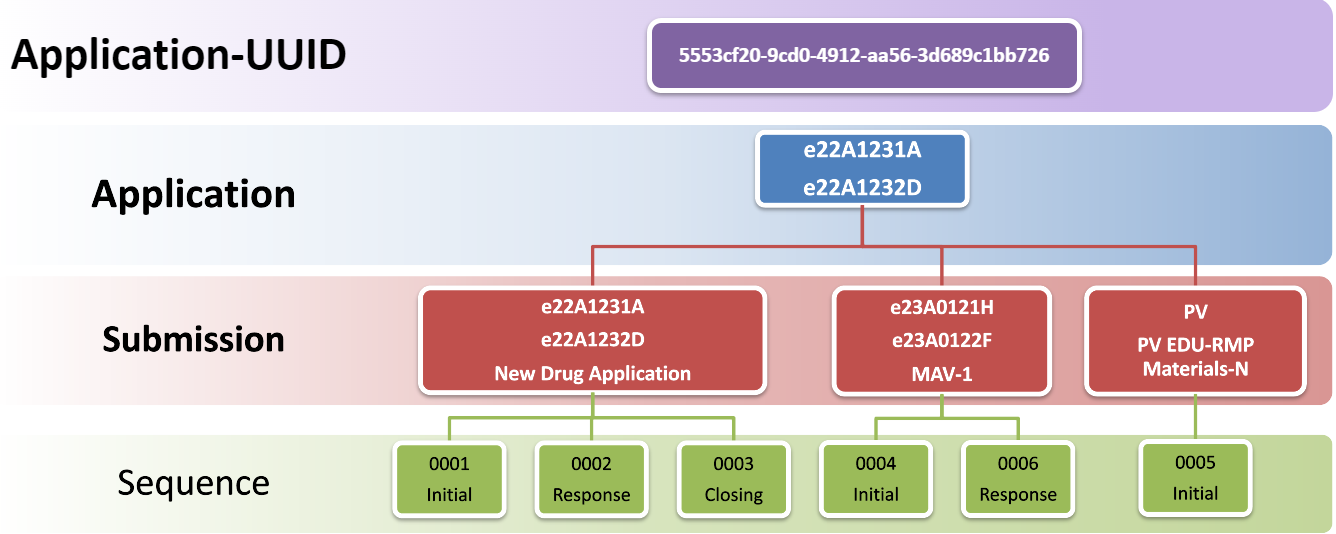


Figure 1 Application, Submission and Sequence Relationship

## Implementation / Transition Plan

The implementation of eCTD in Singapore will go through a multi-phase process starting with an initial phase commencing as soon as the Specifications are released and launched to industry.

The initial Specifications are a collection of best practices adopted from already established eCTD regions and adapted to HSA’s CTD requirements as defined in Guidance on Therapeutic Products Registration in Singapore.

The initial phase will use the SG-HSA Specifications version 1.0. If needed, adjustment to the Specifications, based on experiences gained during the initial phase, are expected approximately 1 year after the launch. Updates to the Specifications can be expected every 2-3 years based on experience from other eCTD regions but will occur as often as needed.

Companies with eCTD capabilities are encouraged to submit in the preferred eCTD format as soon as possible.

# Preparing your Singapore eCTD Application

## The UEN (Unique Entity Number)

The company’s CorpPass UEN is required and should be used to identify the Applicant.

|  |  |
| --- | --- |
| Information | The UEN should be used for all future applications even though the company name changes. If two Applicants with IDs were to merge, one of the 2 IDs would be designated for future use. |

## The Application Number

The first Submission Number issued in PRISM (referred to as Application Number in PRISM) will also function as the Application Number. The first Sequence submitted will always have the same number provided as the Application Number and the Submission Number.

If multiple strengths are combined in a single eCTD Application, then multiple Application Numbers would be issued. All of them should be listed.

A prefix of “e” should be added to the Application Number for all eCTD applications.

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

*Example: PRISM Application Number = 22A1234A, eCTD Application Number = e22A1234A*

For Drug Master File (DMF), the Application Number needs to be requested from HSA.

|  |  |
| --- | --- |
| Information | 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. |

## The Submission Number

The Submission Number is provided by PRISM (referred to as Application Number in PRISM) for all NDA, GDA, MAV, MIV and transfer submissions.

Please enter “DMF” as the Submission Number for all DMF submissions.

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

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

|  |  |
| --- | --- |
| Information | Each new Submission in the eCTD will require a new Submission Number. The Application Number will forever remain the same as it was in the initial Sequence for all future Submissions. |

## Initial Sequence

The initial Sequence 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 be a much higher Sequence, e.g., Transfer of Application where not all Application Numbers are transferred to the Acquiring Applicant. See 3.11 Transfer of Application for more information.

## 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](https://www.hsa.gov.sg/therapeutic-products/guidance-documents):

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

Example: e2212345A 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) that would be expected for your specific Submission Type.

## 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 specificities concerning the eCTD Submission about which the evaluator(s) should be informed, it is highly recommended to provide this information in a structured document that may contain the following sections, as applicable:

* Files referenced at multiple locations within the backbone
* Specifications adhered to
* eCTD attributes
* Hyperlink appearance and strategy
* Bookmark organisation and strategy, or deviations from recommendations
* Particulars of 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

## eCTD Application Folder Naming Convention

When submitting Sequences, the Sequence Folder must be provided in an Application Folder. Name the eCTD Application Folder after the Application Number omitting the last letter if applicable.

Examples: e22a2345, e015-1234 (for DMF)

The most important aspect of the eCTD Application folder is that it is unique and provides flexibilities if and when some but not all products contained in an Application are transferred at a later time to another Applicant.

Some eCTD Applications may have multiple Application Numbers e.g., multiple strengths or second brand products are included in the same eCTD Application. If the numbers are sequential, the range of numbers should be identified. The range indicated does not need to repeat numbers that do not change.

*Examples: e22a2345-8 | e22a2359-62 | e22a2499-502 | e2219998-20002 | etc.*

If multiple Application Numbers are applied to an Application but the numbers are not sequential e.g., some numbers are skipped or numbers were issued at different times, the range should be used ignoring the fact that numbers within the range are not part of the Application.

*Example: e21a2345-2210002*

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

Only the Sequence(s) being submitted should be included in the Application Folder submitted.

|  |  |
| --- | --- |
| Information | Sequences already submitted should not be submitted again. |

## Validating the eCTD Sequence(s)

You should validate the Sequence prior to submitting it. The validation software that is used should validate each eCTD Sequence using the [SG-HSA eCTD Validation Criteria](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

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 issues may result in a business rejection 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 missing "Possible" documents as defined in the [Document Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) 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

|  |  |
| --- | --- |
| Information | 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 Sequence free of validation errors has been provided. For further information or to discuss specific validation errors, please contact HSA.

Sequences with errors will need to be corrected and resubmitted using the same Sequence Number.

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.

If a sequence passes validation with no errors but excessive warnings exist, the Sequence may be rejected in the 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.

Applicants should make every effort to provide a Sequence free of errors and warnings.

## Submitting your eCTD Sequence(s)

Submit your Sequences via the electronic portal.

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

**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 security of the email notifications received by the Applicant via the contact details provided is the responsibility of the Applicant.

# Singapore Regional Considerations

This section includes additional points to consider when compiling your eCTD Sequence to ensure a high-quality Application and an efficient evaluation process.

## 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. In some sections, the source file e.g., Microsoft® (MS) Word or Rich Text Files (RTF) should be provided either instead of the PDF or in addition to the PDF File.

Table 2 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, 1.5, 1.6 or 1.7 except where a specific requirement for a later version is defined. Any PDF with version earlier than 1.4 will result in an error and full rejection of the entire Sequence. |
| 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. |
| 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 5 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. |
| Inherit Zoom | All bookmarks and hyperlinks should have a magnification setting of “Inherit Zoom”. |
| PDF Annotations | PDFs cannot contain any annotations other than bookmarks and hyperlinks. |
| Security | No File Security should be applied, including password protection or limitations to copy content. |
| 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) section 6 PDF Analysis.

Table 3 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 used to create the original file is preferred. |
| Security | No File Security should be applied, including password protection or read-only settings. |

### Module 1

In addition to PDF, as defined by the [ICH eCTD Specification Document](http://estri.ich.org/eCTD/index.htm), we will also accept XML and Microsoft .docx or .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 MS Word, RTF, PDF, or XML related files, should be addressed in the Cover Letter.

In some specified locations, 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 alongside the PDF Files provided. This will allow the content integrity to be secured via MD5 Checksums.

### Module 2 to 5

In addition to the file formats defined for Modules 2 to 5 in the [ICH eCTD Specification](http://estri.ich.org/eCTD/index.htm) and the [ICH Specifications for Study Tagging Files](http://estri.ich.org/STF/index.htm), we will allow comma separated value (CSV) and plain text (TXT) files in Modules 4 and 5 if appropriate.

## Electronic Signatures

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

* Digital signatures.
* Scanned signatures where the documents make up part of the checksum of an eCTD Sequence.
* Scanned documents with wet signatures where the document has then been OCRed.

## Document Navigation Aids

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

### ****Bookmarks****

Use bookmarks to assist us with navigating through PDF documents. We recommend that documents which have multiple headings, sections, tables, figures, references, or appendices AND more than five (5) 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) mandate a check of any documents other than Educational/RMP Materials and Literature References, which have more than five 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.

### ****Table of Contents****

A Table of Contents (TOC) and/or, if appropriate, a Table of Tables, Table of Figures, etc. can be placed on the first page for 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, however the existence of bookmarks is.

### Document Title Pages

Document title pages are not necessary in an eCTD Application and may even have a negative impact on the evaluation efficiency.

### ****Hyperlinks****

Use hyperlinks to aid navigation. A 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 this is not done and 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 later life cycle Sequences. It is therefore advised that the number of hyperlinks applied to Module 3 be limited and should be avoided 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 later life cycle Sequences. It is therefore encouraged that particular attention 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 2.6, 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 – for example a website or email should not be provided. Enough information should be provided to enable a user to search for the link should it no longer be valid.

**Mandatory Hyperlinks**

During validation, the existence of hyperlinks in 1.0.4 Response to Input Request will be confirmed according to the [Validation Criteria](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

Hyperlinks should be created for the sections referenced in the response document where changes were implemented.

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

**Related Information and Guidance**

[ICH eCTD Specifications](http://estri.ich.org/eCTD/index.htm) – Appendix 7

### 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(R4) Guideline on the Organisation of the Common Technical Document for Registration of Pharmaceuticals for Human Use](https://www.ich.org/page/ctd) for the appropriate expected granularity. Follow the lowest level of granularity defined for submitting documents.

|  |  |
| --- | --- |
| Information | 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. |

## Empty or Missing eCTD Sections

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) or P (Possible) 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) for the Submission Type being submitted.
* Do not submit documents for content marked XE (Excluded: Error) or XW (Excluded: Warning) in the [Document Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

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

## Study Tagging Files

We do not require you to provide Study Tagging Files (STFs) for evaluation. You can reuse content submitted in other regions where STFs have been used. If you do this make sure it conforms to the [ICH Specifications for study tagging files](http://estri.ich.org/STF/index.htm).

We will collect data about the number and size of [ICH E3](http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/structure-and-content-of-clinical-study-reports.html) 16.3 CRFs and non ICH E3 documents for informational purposes as part of the [Validation Criteria](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

**Related Information and Guidance**

* [ICH](https://apps.tga.gov.au/downloads/sequence-type.xml) 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.

## 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 programme) should be provided in 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

## Updating eCTD Backbone Attributes

### 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 due to a diluent, etc., "MNF1" and "MNF2" could be used even if in the beginning both components are the same manufacturer. This will allow the Manufacturer for each component to be managed independently.

### Updating Singapore Envelope Information

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

## Reusing Files

All Sequences will be stored according to the Application Number which can then be used to make referencing possible to documents in other Sequences.

|  |  |
| --- | --- |
| Information | 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 eCTD Application (Application Number).

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 2 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 here “…/” is provided 3 times 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 3 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 here “…/” is provided 4 times directing the link out of the “sg”, “m1”, “0002” and Application folders then directing it back down into the “e22a1234” Application folder to the Sequence where the content can be found.

<m1-4-3-clinical>

<leaf ID="N664d6e2d996b4a5b90fc8e2010bbf18a" operation="new"

xlink:href=

"../../../../e22a1234/0001/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 4 Referencing Content used in other Applications

**Related Information and Guidance**

[ICH eCTD Specifications](http://estri.ich.org/eCTD/index.htm) – Appendix 6

## Baseline Submissions

Baseline Submissions should only contain a Cover Letter and, optionally, Note to Evaluator, correspondence with HSA and other additional administrative information. The HSA will not accept any content beyond the Cover Letter and the above-mentioned documents in a Baseline Submission.

Baseline Submissions should be provided when the product is already registered but was approved using a format prior to the introduction of eCTD:

* Paper
* Other Electronic Files (e.g., CTD or ACTD dossier submitted in PRISM and/or CD)

The first sequence of a Baseline Submission will be 0000 as explained in 2.4 Initial Sequence.

A Baseline Submission may also be required as part of the Transfer of Application process if it is not a complete transfer. Application Number(s) used by the previous Applicant will continue to be used. In this case, the Sequence Number containing the baseline information will be included in the next Sequence (not 0000). Please see 3.11 Transfer of Application for more information.

If there is no existing eCTD Application Number, the Application Number for a Baseline Submission should be based on the PRISM Application Number provided for the first activity (e.g. MAV/MIV/Transfer). For the Baseline Submission Number, please indicate “Other” as explained in **2.3 The Submission Number**.

|  |  |
| --- | --- |
| Information | HSA does not require previously submitted and approved content to be submitted again for Baseline Submissions (Submission Type Baseline). The Cover Letter for Baseline Submissions summarises the history of the Application up until the point of the Baseline. |

**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 2.5 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 submissions were submitted
* Indicate if multiple products (e.g., multiple strengths) will be combined into a single eCTD Application
* A tracking table summarising previous 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

## 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) to understand which Submission Types can be combined with each other.

Work Grouping 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

For more information on how to handle Withdrawals and Rejections of Submissions that were part of Work Grouping please see 4.5.2.3 **Submission Withdrawals and Work Grouping** and 4.5.3.1 **Rejected Submissions and Work Grouping**.

**Related Information and Guidance**

* [Submission Type Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – Guidance on which Submission Types can be combined in a single Submission

## Transfer of Application

If products are transferred from one applicant to another (i.e., where there is a change of Applicant), the Application Numbers assigned to the products 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 Application – for example multiple strengths or second brand products. If only part of an Application is being transferred, a Baseline Submission (Submission Type Baseline) should be submitted as the next Sequence, providing:

* All information, in so much as possible, required in a Baseline Submission Cover Letter in **3.9 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 should be considered during any transfer process. The Relinquishing Applicant should provide all Sequences previously submitted to the Acquiring Applicant so that the Application life cycle can be continued, and historical content associated with the evaluation remains intact at the Authority. Even if only a partial transfer is done – meaning not all the Application Numbers included in the Application were transferred, the entire history of the Application should be given to the Acquiring Applicant so that they have a Baseline to relate to and base future variations on.

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

### Basic Requirements for the Relinquishing Applicant

The Relinquishing Applicant should:

* Submit Withdrawals of any open Submissions. These 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.

### ****Basic Requirements for the Acquiring Applicant****

If an Application is acquired that was previously submitted using the preferred 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, Letter of Authorisation and Written Confirmation of Handover of Dossier (i.e., receipt of the entire eCTD).
* Submit a Sequence using.
  + Submission Type: Transfer of Application
  + Sequence Type: Initial

For the detailed documentary requirements, please refer to [Guidance for Change of Registrant of Therapeutic Products](https://www.hsa.gov.sg/therapeutic-products/guidance-documents).

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

### 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.

|  |  |
| --- | --- |
| Information | 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. |

### Scenarios for Transfer of Application

#### Simple Transfer of Application

In a simple transfer, there is either only 1 Application Number, or all Application Numbers included in an Application being transferred. In addition, there are no open Submissions or regulatory activities.

Table 4 Simple Transfer of Application

|  |  |  |
| --- | --- | --- |
| Applicant ABC | Applicant XYZ | Activity/Task |
| 0001 |  | Applicant ABC submits eCTD Application for product with Application Number e22A2345B |
| 0002 |  | Applicant ABC submits responses to HSA’s queries and the Application is approved; the product is registered. |
| 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. |
|  | 0003 | Applicant XYZ submits Submission Transfer of Application to confirm the transfer using Submission Number 22B2345K. |
|  | PRISM | The transfer of the product from Applicant ABC to Applicant XYZ is approved by HSA in PRISM. |
|  | 0004 | Applicant XYZ undertakes business as usual. |

#### Transfer of Application with Withdrawal of Open Submissions

A transfer with open Submissions is not allowed – for example, 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.

Table 5 Transfer of Application with Withdrawal of Open Submissions

|  |  |  |
| --- | --- | --- |
| Applicant ABC | Applicant XYZ | Activity/Task |
| 0001 |  | Applicant ABC submits eCTD Application for product with Application Number e22A2345B. |
| 0002 |  | Applicant ABC submits responses to HSA’s queries and the Application is approved; the product is registered. |
| 0003 |  | Applicant ABC submits a new Submission for MAV1-V with the Sequence Type Initial. |
| 0004 |  | Applicant ABC submits Sequence 0004 to withdraw the MAV1-V using the Sequence Type Withdrawal and Related Sequence 0003. |
| 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. |
|  | 0005 | Applicant XYZ submits Submission Transfer of Application to confirm the transfer using Submission Number 22B2345K. |
|  | PRISM | The transfer of the product from Applicant ABC to Applicant XYZ is approved by HSA in PRISM. |
|  | 0006 | Applicant XYZ undertakes business as usual. |

#### Transfer of Application where not all Application Numbers of an Application are Transferred

If multiple Application Numbers have been grouped into a single Application, it is possible that the Applicant may want to transfer one but not all the strengths or second brand products. In this event, 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 submit a Baseline Submission providing information about the Application as provided by the Relinquishing Applicant.

The identifying Application Folder containing the Application must be unique. The Relinquishing Applicant must continue to use the existing Application Folder without changing it. The Acquiring Application must create a new Application Folder for the product acquired.

Table 6 Transfer of Application where not all Application Numbers of an Application are Transferred

|  |  |  |
| --- | --- | --- |
| Applicant ABC | Applicant XYZ | Activity/Task |
| 0001 |  | Applicant ABC submits eCTD Application for products with Application Numbers e22A2345B and e22A2346K.  The Application folder e22a2345-6 is used. |
| 0002 |  | Applicant ABC submits responses to HSA’s queries and the Application is approved; products are registered. |
| PRISM |  | Applicant ABC initiates the transfer of product e22A2345B to Applicant XYZ in PRISM but not e22A2346K. |
|  | PRISM | Applicant XYZ submits the transfer request in PRISM. PRISM issues a Submission Number (22B2345K) to Applicant XYZ for the Transfer activity. |
|  | 0003 | Applicant XYZ submits a New eCTD Application starting with Sequence 0003 (their first sequence) as Submission Type Transfer of Application to confirm the transfer using the Application Number e22A2345B and Submission Number 22B2345K. The Sequence Type should be set to Initial. The Cover Letter should be provided and any company specific documents, e.g., Company Registration Certificates, should also be updated.  The Application Folder is e22a2345. |
|  | PRISM | The transfer of the product e22A2345B from Applicant ABC to Applicant XYZ is approved by HSA in PRISM. |
|  | 0004 | Applicant XYZ submits Sequence 0004 with Submission Type Baseline and the Submission Number is Other. |
|  | 0005 | Applicant XYZ undertakes business as usual. |
| 0003 |  | Applicant ABC undertakes business as usual but only lists Application Number e22A2346K in the Envelope.  The Application Folder continues to be e22a2345-6. |

# Singapore Module 1 General Architecture

## 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.

### 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:
   1. Module 1 Heading Elements – organising the Singapore Module 1 in accordance with the Specifications.
   2. 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 a perfect validation report is produced.
8. Follow the process to submit your Sequence.

### Stylesheets

The Singapore Module 1 does not have a corresponding stylesheet because modern browsers no longer support the use of locally stored stylesheets e.g., in the “util” folder, as was defined by the ICH Specifications.

## 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="0.9"**  
**xmlns="sg-hsa\_ectd"**  
**xmlns:xsi="**[**http://www.w3.org/2001/XMLSchema-instance**](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**](http://www.w3.org/1999/xlink)**" >**

Figure 5 XML Root Element

## 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 can be used but will not cause validation errors/warnings if not included.

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. For more information on the defined lists, please see The Defined Lists.

### Envelope Overview

Table 7 Overview of the Envelope Elements

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Element | | | | Description | Constraint | Occurrence | Defined List\* |
| sg-envelope | | | | Root element for envelope meta-data |  |  |  |
|  |  | application | | Parent element for Application meta-data indicating Type | Mandatory | Single | X |
|  |  |  | application-uuid | Application Identifier | Mandatory | Single |  |
|  |  |  | application-number | Application Number(s) | Mandatory | Unique |  |
|  |  |  | uen | CorpPass UEN (Unique Entity Number) | Mandatory | Single |  |
|  |  |  | inn | International Non-proprietary Names | 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 meta-data indicating Type | Mandatory | Unique | X |
|  |  |  | submission-number | Submission Number | Mandatory | Unique |  |
|  |  | sequence | | Parent element for Sequence meta-data indicating Type | Mandatory | Single | X |
|  |  |  | sequence-description | Sequence Description | Mandatory | Single |  |
|  |  |  | sequence-date | Sequence Date of Submission | Mandatory | Single |  |
|  |  |  | sequence-number | Sequence Number | Mandatory | Single |  |
|  |  |  | related-sequence-number | Related Sequence Number | Mandatory | Single |  |
|  |  | contact | | Parent element for Contact meta-data indicating Type | Mandatory | Multiple | X |
|  |  |  | contact-name | Contact Name | Mandatory | Single |  |
|  |  |  | contact-email | Contact Email | Mandatory | Single |  |
|  |  |  | contact-phone | Contact Phone | Optional | Single |  |

### 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.

<sg-envelope>

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

<application-uuid>5553cf20-9cd0-4912-aa56-3d689c1bb726</application-uuid>

<application-number>e21A2345K</application-number>

<application-number>e21A2346P</application-number>

<application-number>e21A2347B</application-number>

<uen>202212345A</uen>

<inn>dsabc</inn>

<inn>dsxyz</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 400mg/50mg</proprietary-name>

<proprietary-name>singaPill Tablet 200mg/50mg</proprietary-name>

<proprietary-name>singaPill Tablet 100mg/50mg</proprietary-name>

</application>

<submission code-version="1.0" code="sub-type-8">

<submission-number>2212378K</submission-number>

<submission-number>2212379P</submission-number>

<submission-number>2212380B</submission-number>

</submission>

<submission code-version="1.0" code="sub-type-12">

<submission-number>2223792R</submission-number>

<submission-number>2223793S</submission-number>

<submission-number>2223794C</submission-number>

</submission>

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

<sequence-description>PIL Update & administrative change of company address</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 6 Sample Code for Submitting Multiple Values in the Envelope

### 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 7 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-N</item>

Figure 8 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 6 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 at the link below. 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 always be valid for 6 months after they have been superseded.

**Related Information and Guidance**

* [eCTD Defined Lists](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – Official defined list for the Singapore eCTD Elements

### Envelope Attributes

#### 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.

The Application Type should be indicated for the Application.

Application Type is a coded list. The code should be indicated in the Envelope.

Example: app-type-1

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

Figure 9 Envelope Element: Application Type

**Related Information and Guidance**

* [application-type](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – Official defined list for Application Type

#### Application Identifier

A universally unique identifier (UUID) as specified by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834-8:2005.

It is a 128-bit label and is unique for practical purposes when generated according to the standard methods.

The same UUID will be used for all Sequences of an eCTD application and cannot ever be changed.

Example: 5553cf20-9cd0-4912-aa56-3d689c1bb726

<application-uuid>5553cf20-9cd0-4912-aa56-3d689c1bb726</application-uuid>

Figure 10 Envelope Element: Application Identifier

#### Application Number

Each product will be assigned a unique Application Number. The Application Number is a combination of

* the letter "e" for eCTDs
* the submission number for the very first eCTD Sequence submitted as provided by PRISM (referred to as Application Number in PRISM)

An Application Number will be required for:

* Each strength for products with multiple strengths.
* Each second brand product, also – for example for all strengths of the second brand product.

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, but different pharmaceutical forms should be in separate eCTD Applications.

Table 8 Application Numbers for Different Strengths and Second Brand Products

|  |  |  |  |
| --- | --- | --- | --- |
| Product | Strength | Form | Application Number |
| singaPill HGC | 200mg | Film Coated Tablet | e22A2341A |
| singaPill HGC HS | 100mg | Film Coated Tablet | e22A2342D |
| singaPill HGC DS | 400mg | Film Coated Tablet | e22A2343G |
| genPill\* HGC | 200mg | Film Coated Tablet | e22A2344J |
| genPill\* HGC HS | 100mg | Film Coated Tablet | e22A2345L |
| genPill\* HGC DS | 400mg | Film Coated Tablet | e22A2346P |

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

Enter the Application Number assigned and use it to form the eCTD Application folder which contains Sequence folders as described in 2.7 eCTD Application Folder Naming Convention.

See 2.2 The Application Number for more information on Application Numbers.

Example: e22A2345B

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

Figure 11 Envelope Element: Application Number

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope.

#### Unique Entity Number (UEN)

The Applicant’s UEN as used in CorpPass should be entered as a unique identifier for the Applicant.

Example: 202212345A

<uen>202212345A</uen>

Figure 12 Envelope Element: Applicant’s UEN

#### International Non-proprietary Name(s) (INN)

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

Example: amoxicillin

<inn>amoxicillin</inn>

Figure 13 Envelope Element: INN

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

#### Product Type

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 14 Envelope Element: Product Type

#### DMF Number

If a DMF is referenced in the current eCTD application, the DMF Number as issued should be added. Please note that a corresponding Letter of Access should be provided in section 1.5.3.1.

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

Figure 15 Envelope Element: DMF Number

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

#### PMF Number

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

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

Figure 16 Envelope Element: DMF Number

See the example XML code in section 4.3.2 Submitting Multiple Values in the Envelope

#### Proprietary Name(s)

The name as proposed or registered in PRISM.

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

*Example: singaPill*

*Example: amoxicillin DMF Pharma*

<proprietary-name>singaPill</proprietary-name>

Figure 17 Envelope Element: Proprietary Names

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

#### SIN Number

The Singapore registration number. This is an optional field and should be left blank for new Applications. Once the product is registered, the registration number should be provided here. If multiple registration numbers are associated with the eCTD Application, all registration numbers should be provided.

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

Figure 18 Envelope Element: SIN Number

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

#### 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

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.

|  |  |
| --- | --- |
| Information | Multiple Submissions of the same Submission Type may not be combined. Instead, multiple Submission Numbers should be listed within a single Submission. |

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.

Submission Type is a coded list. The code should be indicated in the Envelope.

Example: sub-type-1

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

Figure 19 Envelope Element: Submission Type

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

**Related Information and Guidance**

* [submission-type](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – Official defined list for Submission Type
* [Submission Type Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – A summary of the allowed combinations of Submission Types in a single Sequence.

#### Submission Number(s)

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

See 2.3 The Submission Number for more information on Submission Numbers.

If appropriate, multiple Submission Numbers can be given 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 20 Envelope Element: Submission Number

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

#### 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.

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.

|  |  |
| --- | --- |
| Information | Please note that the Closing Information Sequence Type should only be used to provide information under an Approval Pending or Approved situation and only with Module 1 content. Subsequent to a Closing Information Sequence Type, the only allowable Sequence Type is Closing Information. |

Sequence Type is a coded list. The code should be indicated in the Envelope.

Example (Initial): seq-type-1

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

Figure 21 Envelope Element: Sequence Type

**Related Information and Guidance**

* [sequence](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions)-type – Official defined list for Sequence Type

#### 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** – Don’t write an extensive description, this should be done 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. Provide more precise details but keep in short.
* **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 22 Envelope Element: Sequence Description

#### Sequence Date

The Sequence Date is a date field indicating the date the Sequence is submitted. This date should correlate as closely as possible with the date on the Cover Letter and in the Application Form but do not need 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 should check to ensure 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:* 2022-05-20

<sequence-date>2022-05-20</sequence-date>

Figure 23 Envelope Element: Sequence Date

#### Sequence Number

Four-digit number matching the Sequence folder being submitted.

New Applications with Submissions starting with a “New Drug…” or “Generic Drug…” Submission Type should start with the Sequence 0001.

Baseline Submissions should start with the Sequence 0000.

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

*Example:* 0011

<sequence-number>0001</sequence-number>

Figure 24 Envelope Element: Sequence Number

#### 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 9 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 | **0004** | MAV1-V | Initial |
| 0005 | **0005** | MIV2-DnT | Initial |
| 0006 | **0006** | MIV1-PI | Initial |
| 0007 | **0004** | MAV1-V | Supplementary Information |
| 0008 | **0004** | MAV1-V | Response |
| 0009 | **0004** | MAV1-V | Response |
| 0010 | **0006** | 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.

The Related Sequence Number should be approached similar to the Submission ID described in the [US regional specification 2.5](http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm153574.htm) and the Related Sequence Number in the AU regional specifications 3.1

*Example:* 0001

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

Figure 25 Envelope Element: Related Sequence Number

#### Contact Type

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.

The Contact element section contains all the Contact related information for a particular contact. The Contact Type must be indicated for the Contact element. Contact Type is a coded list. The code should be indicated in the Envelope.

Example (Regulatory Contact): contact-type-1

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

Figure 26 Envelope Element: Contact Type

See the example XML code in 4.3.2 Submitting Multiple Values in the Envelope

**Related Information and Guidance**

* [contact-type](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions) – Official defined list for Contact Type

#### 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 27 Envelope Element: Contact Name

#### Contact Email

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

Example: [sarah.tan@pharma-inc.co.sg](mailto:sarah.tan@pharma-inc.co.sg)

<contact-email>[sarah.tan@pharma-inc.co.sg](mailto:sarah.tan@pharma-inc.co.sg)</contact-email>

Figure 28 Envelope Element: Contact Email

#### 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.

Example: +65 1234 5678

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

Figure 29 Envelope Element: Contact Phone

## Heading and Leaf Elements

### Module 1 Heading Elements

The next 10 tables list the Heading elements of the Singapore eCTD Module 1 v0.9.

Content under the following Headings should be provided when required, as defined in the [Document Matrix](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

Please refer to the [Guidance on Therapeutic Products Registration in Singapore](https://www.hsa.gov.sg/therapeutic-products/guidance-documents) 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](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

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

Table 10 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 11 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 12 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 13 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 14 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 | DMF Submission Form | m1-5-2-dmf-submission-form |
| 1.5.3 | Letter of Access | m1-5-3-loaccess |
| 1.5.3.1 | DMF Letter of Access | m1-5-3-1-dmf-loaccess |
| 1.5.3.2 | PMF Letter of Access | m1-5-3-2-pmf-loaccess |
| 1.5.4 | EMA Certificate for Plasma Master File (PMF) | m1-5-4-ema-pmf |
| 1.5.5 | Certificate of Suitability (CEP) | m1-5-5-cep |

Table 15 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 16 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 17 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 18 Heading Elements 1.10 – 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 19 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 |

### 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).

|  |  |
| --- | --- |
| Information | 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 30 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.
* **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.

|  |  |
| --- | --- |
| Information | **Operation** – Append should only be used in connection with Study Tagging Files. |

### 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.

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 repeat the optional node extension and Leaf elements as required. The schema will ensure the checksum-type attribute contains either "MD5" or "md5".

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

|  |  |
| --- | --- |
| Information | Note that if node extensions are not used for clinical studies, an error 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 not for the lowest level of the eCTD Structure

|  |  |
| --- | --- |
| Information | Note that using node extensions where ICH subheadings already exist or at a level that is not the lowest level will result in an error 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.

### 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.

#### 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.

#### 3.2.R Regional Information

Leaf elements in 3.2.R Regional Information heading must be provided using node extensions. PDF files are not allowed as leaf elements directly under 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.

|  |  |
| --- | --- |
| Information | 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.

## 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.

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

### Specific Life Cycle Operations for Singapore

The nodes with specific life cycle operations mandated for a Singapore eCTD are summarised in Table 20 Nodes with Specific Life Cycle Operations. Adherence to these specific requirements will be validated.

Table 20 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 |
| 1.2 | **Administrative Information** |  |  |
| 1.2.2\*\* | Checklists | New | Error |
| 1.2.4 | Table of Summary of Changes | New | Error |
| 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.

Product Information for New Applications should be placed in the Approved section. The Leaf title should clearly state that it is the proposed product information. Once approved, the proposed content should be replaced with the approved content and the Leaf title should be updated to indicate it has been approved and the date of approval.

Once Product Information is approved, any further proposed changes should be submitted in the Clean Proposed section and an annotated copy of the proposals should be placed in the Annotated section. A copy of the current Approved Product Information should be provided in the Approved section by referencing to the earlier Sequence.

Once Proposed changes presented in Clean Proposed have been approved, a “Closing” Sequence should be provided that transfers the content from Clean to Approved. Only reference to the content provided in the earlier sequence under Clean Proposed should be provided, the physical file should not be provided again. Please see 3.8 Reusing Files for more information on reusing content already submitted.

### Life Cycle Operations for a Withdrawal

There are two types of withdrawals:

* **Application Withdrawal** – The withdrawal of an entire eCTD Application.
* **Submission Withdrawal** – The withdrawal of a Submission still under evaluation. The product Application should remain registered.

#### ****Application Withdrawal****

|  |  |
| --- | --- |
| Information | Application withdrawal should only be done once the product registration is cancelled in PRISM. In the case of a Drug Master File, withdrawal is only possible once the DMF is no longer being referenced/used. |

When withdrawing an entire product life cycle history, the following attributes should be applied in the envelope element:

* The Submission Type should be set to “Application Withdrawal”.
* The Sequence Type should be set to “Initial”.
* The Sequence Description should be set to “Cancellation”.
* Application Withdrawal should be considered a new Submission so the Sequence and the Related Sequence should be set to the next available Sequence.

The following life cycle rules should be applied:

* A Cover Letter should be included as “New” and explain why the eCTD Application is being withdrawn.
* No further content or life cycle is required.

#### ****Submission Withdrawal****

When withdrawing a Submission, 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 still under evaluation so the Related Sequence should be set to the “Initial” Sequence of the Submission.

The following life cycle rules should be applied:

* The Cover Letter should be the only document submitted as New.
* Content that was replaced by the Submission must be reset referencing the document that was previously referenced in the earlier Sequence using the Replace operation. The document should NOT be provided again.
* Content that was added as New in the Submission must be removed using the Delete operation.
* If Work Grouping was done in the first Sequence, see **Submission Withdrawals and Work Grouping** on how to address the reactivation of those activities. DO NOT remove any content belonging to the other Submissions using the Delete operation.

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

#### ****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, it will technically show up as a withdrawal of all Submissions combined in the Initial Sequence of the Submission.

If only part 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 second 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.

### 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.

#### Rejected Submissions and Work Grouping

If a Submission is rejected, it will technically show up as a rejection of all Submissions combined in the Initial Sequence of the Submission if Work Grouping was used.

An additional Sequence should be submitted as a New Initial 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 3.8 Reusing Files.

## Files and Folders

### 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 21 Minimum Naming Conventions Matrix.
* No file name can end with “.p” as this is seen as a security risk by the SG-HSA IT policy. E.g., “introduction.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.

Table 21 Minimum Naming Conventions Matrix

| **Folders** | | | | **Files** | **Description** |
| --- | --- | --- | --- | --- | --- |
| e22a2345 | | | | | Application folder with Application Number e.g., e12a1234, e015-1234 |
|  | 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[[1]](#footnote-2) 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 | | Style Sheet Folder in Accordance with ICH |
|  |  |  |  | ectd-2-0.xsl | ICH style Sheet for Modules 2 to 5 |
|  |  | 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.

### Folder and File Name – Path Length

Ensure the overall length of the folder and file name path, starting from the Sequence Number, does not exceed 180 characters, for any file in any module.

### Source Documents

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

Table 22 Source File Requirements

|  |  |
| --- | --- |
| Requirement | Requirement Details |
| 1.2.2 Checklists | MS Word Only |
| 1.3.3 Package Insert (PI) | MS Word File in addition to the PDF |
| 1.3.4 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 |

# eCTD Preparation Tools

## 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.

|  |  |
| --- | --- |
| Information | 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 and ongoing 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, they evaluate the technical content of the Sequence for the eCTD Application. We recommend you use a validation tool that:

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

# 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 23 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)** |
| 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 | DMF Submission Form [DMF NUMBER] |
| 1.5.3 | **Letter of Access** |
| 1.5.3.1 | DMF Letter of Access [SUBSTANCE] [DMF NUMBER] [DMF HOLDER/COMPANY] |
| 1.5.3.2 | PMF Letter of Access [PMF NUMBER] [PMF HOLDER/COMPANY] |
| 1.5.4 | EMA PMF [PMF HOLDER] |
| 1.5.5 | 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** |
| 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** |
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| 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 |
| 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.4.0 | Control Strategy Summary |
| 3.2.S.4.1 | **Specification** |
| 3.2.S.4.2.1 | Analytical Procedure [DESCRIPTION] |
| 3.2.S.4.3.1 | Validation of Analytical Procedure/Method/Assay [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.3.1.1 | 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 |
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| 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 |
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| 3.2.P.5 | **Control of Drug Product** |
| 3.2.P.5.0 | Control Strategy Summary |
| 3.2.P.5.1 | **Specification** |
| 3.2.P.5.2.1 | Analytical Procedure [DESCRIPTION] |
| 3.2.P.5.2.1 | Method [DESCRIPTION] |
| 3.2.P.5.2.1 | Assay [DESCRIPTION] |
| 3.2.P.5.3.1 | Validation of Analytical Procedure/Method/Assay [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] |
|  | **Excipient** |
| 3.2.A.3 | Excipient [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] |
| 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] |
| 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 |

# 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 |  |  |  |
|  |  | 1.5.3 | 1.5.3.1 |  |  |
|  |  |  | 1.5.3.2 |  |  |
|  |  | 1.5.4 |  |  |  |
|  |  | 1.5.5 |  |  |  |
|  | 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 |  |  |

# Change Control

The following documents were referenced during the creation of this specification:

* eCTD ECOWAS Module 1 and Regional Information
* eCTD AU Module 1 and Regional Information
* [EU Module 1 eCTD Specification](http://esubmission.ema.europa.eu/eumodule1/docs/EU%20M1%201.4.1/EU%20M1%20v141_Spec%20_Nov2011_FINAL.pdf)
* GCC Module 1 eCTD Specification
* [The eCTD Backbone Files Specification for US Module 1](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf)
* ICH eCTD Specifications v3.2.2
* ICH eCTD Specifications v4.0

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
* Updates to the Processes – Automation

We will provide a practical timeframe for future changes to minimise impact on industry. In general, a transition time of at least 6 months is provided for migration to new Specifications.

If you have any feedback, comments, or questions, please visit [HSA | Electronic Common Technical Document (ECTD) Submissions](https://www.hsa.gov.sg/therapeutic-products/register/ectd-submissions).

# Version History

**Versioning Guide**

Versions to the Specifications will be handled as follows:

* Major Versions will be triggered by changes in the Envelope or Heading Elements e.g., version 1.0, 2.0, 3.0.
* Minor Versions will be triggered by all other changes that require updates to the Schema e.g., version 1.1, 1.2, 1.3.
* Changes in the Specification document that do not trigger changes to the Schema will be identified by a number suffixing the minor version number e.g., version 1.01, 1.02, 1.03.
* All Major Versions will begin with the minor version 0 and no document version number will be applied until changes to the document have been issued. For both the minor versions and document changes the version number will be a single character running from 1-9 and then a-z if necessary.

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Description of Change | Author | Effective Date |
| 0.9 | Initial version for industry review | Singapore eCTD Project Team | 2023-05-02 |
| 1.0 | Initial version | Singapore eCTD Project Team | 2023-MM-DD |

1. Document Type Definition (DTD) - A document type definition is a set of markup declarations that It defines 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. [↑](#footnote-ref-2)