ZA-SAHPRA CTD eSubmission Specification

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1. Introduction

The CTD eSubmission Specification is a temporary solution for certain applications to be used while companies have time to implement an Electronic Common Technical Document (eCTD) solution. Please pay close attention to the timelines set forth in the SAHPRA Roadmap. Companies should not see this Specification as an alternative to eCTD long-term and not as an alternative for Biological and Orthodox submissions, as they are mandatory to be submitted in eCTD format. Companies should alert SAHPRA on their plans to implement eCTD.

eCTD is SAHPRA's preferred format as it enables a more efficient evaluation and provides a means to maintain a better overview of Applications over time with the use of life cycle operations which are absent from eSubmissions.

This Specification should be read together with the eCTD Specification because much of the information in the eCTD Specification also applies to the eSubmissions when possible. Much of this document will reference the eCTD Specification when appropriate.

This document applies to all CTD Applications not submitted in eCTD format. 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 and a varying degree of detail may be required in Modules 1-3. Guidance on what content should be provided for the different Submission Types is provided in the Document Matrix.

This SAHPRA eSubmission Specification is like NeeS (Non-eCTD electronic Submission) implemented in other regions – for example EU, Australia and GCC – but has some key differences such as:

- There are no requirements for PDF TOCs. SAHPRA will be using a utility that will automatically build an XML backbone based on folder and file names. No files submitted by the applicants will be altered during the creation of the backbone which will act as an electronic navigation and TOC for each Sequence submitted.
- There is a requirement to provide an envelope.xml trigger file along with the sequence. Please refer to the section on the SAHPRA envelope.xml trigger file.

This document contains:

- guidance on the structure of a South African CTD eSubmission Application; and
- guidance on creating and validating your South African CTD eSubmission Sequences.

Version 3.0 of the Specifications should be read in combination with:

- 2.22 ZA-SAHPRA eCTD Validation Criteria
- 2.28 ZA-SAHPRA eCTD Q&A Document
- 2.26 ZA-SAHPRA eCTD Roadmap
- 2.21 ZA-SAHPRA eCTD Specification and Guidance for Module 1 and Regional Information
- 2.24 ZA-SAHPRA Guidance for the Submission of the South African CTD / eCTD General - Module 1 and Regional Information

All documents are provided on the SAHPRA eCTD Website. SAHPRA eCTD (https://ectd.sahpra.org.za/)

1.1. Background

The specification for the eCTD is based on content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organisation of modules, sections, and documents. The structure and level of detail specified in the CTD have been used as the basis for defining the eCTD structure and content but, where appropriate, additional details have been developed within the eCTD specification.

The philosophy of the eCTD is to use open standards. Open standards, including proprietary standards which through their widespread use can be considered de facto standards, are deemed to be appropriate in general.

1.2. Scope

The Scope is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

1.3. Comment about ICH eCTD version 3.2.2 and 4.0

SAHPRA is currently using eCTD Specifications based on ICH 3.2.2 however the long-term plan is to start adopting 4.0 by 2030. eCTD Solutions should therefore ideally be able to support both versions long term.

1.4. Technical Requirements

The Technical Requirements are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

1.5. Terminology

The Terminology is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

2. Business Protocol: Preparing your CTD eSubmission Application

2.1. The SAHPRA Application Portal

The SAHPRA Application Portal usage is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

2.2. Initial Sequence

The Initial Sequence is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

2.3. Preparing the CTD eSubmission Letter of Application

All requirements for the eCTD Letter of Application apply to the eSubmission Letter of Application. In addition to the eCTD requirements, however, a statement should be added to all eSubmission Letter of Application, that updates SAHPRA on the progress with moving to eCTD and in line with the roadmap related to this product category. This statement should include the following:

- indicate the eCTD Implementation phase your company is currently in (if applicable and in line with the roadmap related to this product category) :

Table 1 eCTD Implementation Phases

Phase	Phase Title	Phase Description
Phase 0	Not Yet Started	eCTD Implementation has not yet started
Phase 1	Requirement Analysis	Understanding the Requirements
Phase 2	User Requirement Collection	Defining the Functionality Required specific to the Company and Regulatory Department
Phase 3	Solution Analysis	Looking at Solution Options, Engaging with Solution Providers, Looking at Outsourcing Options, Developing In-house
Phase 4	Solution Selection & Budgeting	Identification of Solution and Budgeting for Solution Implementation
Phase 5	Solution Implementation	Installation, Validation and Training of Selected Solution

- indicate your estimated timeline until when you will be able to begin submitting in eCTD.
- if your estimated timeline has changed to a later date than indicated in earlier Sequences, provide a brief high-level explanation why the delay has occurred.
- provide a statement acknowledging your understanding that eSubmission is not the preferred format.
- provide a statement indicating you will begin providing Sequences in eCTD format before the eSubmission end of life for your product category. The deadline date must be included in the statement.

Example:
[COMPANY] is currently in phase 1 of eCTD implementation. We expect to be able to submit eCTD by [DATE]. We understand that eSubmission is not the preferred format and we confirm

our commitment to begin submitting in the eCTD format before the eSubmission end of life deadline on [DATE].

2.4. Preparing the Note to Evaluator

The Note to Evaluator is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

2.5. CTD eSubmission Application Folder Naming Convention

The Application Folder Naming Convention is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

2.6. Validating the eSubmission Sequence(s)

The Validation Process is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

There are some additional checks specific to eSubmissions. Please refer to the SAHPRA eSubmission Validation Criteria, for more information on eSubmission Validation which has been integrated into the existing Validation Criteria.

The validation requirements of eSubmissions are almost identical to eCTD with the exception that life cycle management is not checked (because it does not exist in eSubmissions) and content re-use is not allowed.

2.7. Submitting your CTD eSubmission Sequence(s)

The process for Submitting your eSubmission Sequences is the same as described in the SAHPRA eCTD Specifications for eCTDs. Please refer to the Specifications, same section, for more information.

3. South African Regional Considerations

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

3.1. File Formats

The File Formats, Validated PDF Requirements, General Source File Requirements for the South African Module 1 and the ICH Modules 2-5 are the same as described in the SAHPRA eCTD Specifications with the exception that Study Tagging Files (STFs) are not allowed in eSubmissions. Please refer to the Specifications, same sections, for more information.

3.2. Electronic Signatures

The handling of Electronic Signatures is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same section, for more information.

3.3. Document Navigation Aids

The requirements for Document Navigation Aids are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

3.4. Empty or Missing CTD Sections

The handling of Empty or Missing CTD Sections is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

3.5. Study Tagging Files

Study Tagging Files are a product of eCTD Applications and cannot be provided in an eSubmission. Only the content defined in the ICH E3 Structure and Content of Clinical Study Reports should be included when appropriate. Case Report Forms and Individual Patient Listings should be provided in the CTD section 5.3.7 when appropriate.

3.6. Submission of PBRER/PSUR and RMP Reports

Periodic benefit-risk evaluation reports (PBRER) or periodic safety update reports (PSUR) and other risk management plan (RMP) reports (e.g., PV-related safety studies, etc.) should be provided in 5.3.6 using additional folders.

For guidance on how best to title the folders, please see examples below.

Examples of Folders:
PSUR 2024-01-30 to 2024-06-30
PBRER 2024-01-30 to 2024-06-30
RMP Report 2024-06-30

3.7. Updating Attribute Specific Folders

3.7.1. Updating Folder Names based on ICH eCTD Attributes

Updating Folder Names based on ICH eCTD Attributes

The following sections in the CTD structure have a specified folder structure in the eSubmission file and folder setup.

Table 2 Attribute Specific Subfolders

Section	Section Title	Attribute Specific Subfolders
3.2.S	Drug Substance	Substance-Manufacturer
3.2.P	Drug Product	Product-Dosage-Manufacturer
3.2.P.4	Control of Excipients	Excipient
3.2.A.3	Excipients	Excipient
5.3	All Clinical Study Reports	Study ID-Study Description
5.3.5	Reports of Efficacy and Safety Studies	Indication

To ensure consistency between the Sequences, the attributes specific subfolders should not be altered over time, 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 as folder name e.g., "mnf" and the manufacturer(s) represented by the variable can be declared and maintained in the Note to Evaluator. We recommend that you do not include the name of manufacturers into the folder names for the "P" section.

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.

A Warning will result in the validation report if folders are introduced that are not unique in later life cycle Sequences. This could lead to rejection of the eSubmission Sequence if the need of unique folder is not substantiated by the Submission Type.

Keep in mind the restrictions on folder length (64 characters) and total path length (180 characters) when creating the subfolders. Values should be abbreviated. They need to be short, precise, and distinguishing. Folder and path lengths are validated.

3.7.2. Updating the SAHPRA envelope.xml Trigger File

The Trigger File will be created automatically based on the information provided in the Portal. Information used in the Trigger File can be updated in the Portal, it is allowed to update during the life cycle as is necessary to reflect changes in the metadata - for example, changing, adding and removing product names.

3.8. Reusing Files

File reuse is not allowed in eSubmissions. Files should be provided in all sections where they would be referenced. A detailed listing of all files that appear multiple time in different locations in the eSubmission should be included in the Note to Evaluator. In addition, an entry in the Electronic Declaration Document should be added that will indicate that all copies of the content provided in multiple locations are identical.

The inability to reuse content reduces the efficiency of the evaluation and is one of the reasons why eCTDs are the preferred format.

3.9. Baseline Submissions

Baseline Submissions should contain all application content previously evaluated and approved.

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

- Paper
- Other Electronic Files (e.g., unstructured documents provided for minor variations)

Baseline Submissions are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

Note that if you have provided previous sequences in the former eSubmission NeeS format, you can continue with the life cycle without providing an additional baseline if a complete baseline has already been provided in the former format. New sequences should be valid with new 3.0 specifications.

3.10. Work Grouping

Work Grouping is not allowed for eSubmissions. It is expected that a separate Sequence will be submitted for each Submission. Combinations of multiple Submissions in a single Sequence complicates the life cycle and becomes difficult to manage without the life cycle operations associated with eCTD Applications.

If multiple Submissions are listed in the envelope.xml file for eSubmissions, a validation Error will occur.

3.11. Splitting the CTD eSubmission Application

The process for Splitting the CTD eSubmission Application is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

3.12. Transfer of Application

The process for the Transfer of Application is the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

4. South African eSubmission General Architecture

An eSubmission relies on a structured and predictable approach to presentation content. The structured presentation enables a validation of content which increases the quality of applications and saves time during the screening and evaluation process.

4.1. eSubmission Folders

The CTD structure can be presented in electronic form using the ICH recommended folders and file names in the ICH eCTD Specifications. Since SAHPRA does not have a recommended naming convention for its eCTD Module 1, a folder naming convention has been specified in the eSubmission Folder and File Names tab of the SAHPRA eCTD Validation Criteria v3.1 which should be followed for all eSubmissions. This is consistent with naming conventions used under the 2.1 specifications where content has not been changed.

The folders for the SAHPRA Module 1 are based on the Heading Elements of the eCTD Specification and are designed to promote a logical order for the folders when displayed in the Windows Explorer®. A leading “0” has been added in front of the second level section number to allow proper sorting of content in the order intended. For example, the folder for 1.2 has been designated as 102 in the naming convention.

As an exception, the folders created for Module 5 study reports should be made up of the Study ID (Study Number) along with a short, precise, and distinguishing description. This will help the evaluator differentiate between the studies provided without having to open them.

A zip file with the empty folder structure is available on the SAHPRA eCTD Website for download. This is meant to simplify the creation of the necessary folder structure so that applicants can simply fill the folder structure with the necessary files.

The attributes specific folders listed in section **3.7.1 Updating Folder Names based on ICH eCTD Attributes** must follow the eCTD rules on naming conventions detailed in the ICH eCTD Specifications. These rules forbid:

- the use of any spaces
- the use of any special characters other than the hyphen “-“
- the use of any CAPITAL letters

In addition, values placed in the attribute specific folders should be abbreviated and the applicant should take care to ensure that folder names do not exceed 64 characters.

Applicants should delete any empty folders from their Sequence, only folders with content should be included.

Additional folder structures beyond the defined structure are not allowed. Use the variable filenames to group and identify like content you want to organise together.

Related Information and Guidance

- SAHPRA eCTD Validation Criteria

The following will result in Validation Errors

- The use of spaces, special characters, and capital letters in folder names
- Attribute specific folders with more than 64 characters
- Empty folders
- Additional Folder Structures beyond the defined structure

4.2. eSubmission File Names

The file names used in Modules 2-5 should conform to those provided in the eSubmission Folder and File Names tab of the SAHPRA eCTD Validation Criteria which are in line with those recommended by ICH in the ICH eCTD Specifications with the exceptions listed below.

- **Literature References** – ICH refers to a naming convention for references placed in 3.3, 4.3 and 5.4 as “reference-1.pdf”, “reference-2”, etc. This is not helpful or intuitive for the evaluator. Instead, the author and year should be used. References in the documents of the Application to the Literature References should refer to the author and year as used in the file names.
- **Study Reports** – ICH refers to a naming convention for all studies in Module 4.2 and 5.3 as “study-report-1”, study-report-2”, etc. This is not helpful or intuitive for the evaluator. Instead, the Study ID (Study Number) should be used along with a short, precise, and distinguishing description. In Module 5 study reports where a multiple file approach has been taken, the description should clearly identify the study component, ideally in line with the ICH E3 Structure and Content of Clinical Study Reports guidance.

Since SAHPRA does not have a recommended naming convention for its eCTD Module 1, a file naming convention has been specified in the eSubmission Folder and File Names tab of the SAHPRA eCTD Validation Criteria which should be followed for all eSubmissions.

The optional PDF TOCs are indicated in Blue. If you are using a system that creates eSubmissions with PDF TOCs, your system likely is also able to create eCTDs. Please investigate and move to the preferred eCTD format as soon as possible.

PDF TOCs are not necessary in the SAHPRA eSubmission

Variable Filename Components

Variable Filename Components in the ICH eCTD Specifications usually follow the concept of fixed filename followed by a unique number starting with 1 to ensure that each filename is unique. Numbered files do not provide helpful or intuitive information for the evaluator so meaningful variables should be provided instead.

Do not use filenames like:

- analytical-procedure-1.pdf
- analytical-procedure-2.pdf
- analytical-procedure-3.pdf

Do use filenames like:

- analytical-procedure-id.pdf
- analytical-procedure-limitimpurity.pdf
- analytical-procedure-qualityimpurity.pdf

The ICH numbering system is appropriate for files provided in the eCTD format because the eCTD provides an alternative Title element in the XML backbone. The Title is descriptive, and it is all the evaluator sees. Evaluators do not see the actual filename in an eCTD.

The ICH numbering system is NOT appropriate for files provided in the eSubmission format because the evaluator only sees the filename to identify the content. No alternate Title element exists.

Filename variables are validated for eSubmissions and if a numbered approach is used, validation warnings will occur because this will negatively affect the evaluation efficiency.

NOTE: The numbered approach is accepted in eCTD applications where emphasis is placed on providing descriptive leaf titles.

Related Information and Guidance

- SAHPRA eCTD Validation Criteria
- ICH E3 Structure and Content of Clinical Study Reports guidance

4.3. eSubmission envelope.xml Trigger File

The SAHPRA Application Portal will automatically create the envelope.xml file required or eSubmissions without the need for an additional software solution.

Refer to the SAHPRA eCTD Specifications for more information on Envelope Elements.

The only difference between the eCTD Envelope and the eSubmission Envelope is that the eSubmission Envelope does not allow multiple Submissions to be combined in a single Sequence. A separate Sequence must be submitted for each Submission in the eSubmission format.

If multiple Submissions are listed in the envelope.xml file for eSubmissions, a validation Error will occur.

Related Information and Guidance

- Sample envelope.xml

4.4. eSubmission Headings

Refer to the SAHPRA eCTD Specifications for more information on Headings. The eCTD Headings should be integrated into the documents submitted to make clear identification of the content as evaluator friendly as possible.

Comprehensive Table of Content of Life Cycle Operations

All Headings are the same as in the eCTD with the exception that eSubmissions have an additional heading:

Table 3 Additional Heading for eSubmission 1.1 – Table of Contents

Section ID	Title
1.1	**Table of Life Cycle Operations**

The Table of Life Cycle Operations is designed to provide the evaluator the ability to manually put together information automatically provided by eCTD Applications. The deeper into the life cycle the Application progresses i.e., the more Sequences that are submitted, the more important the table becomes for the evaluation.

The table gives the evaluator information on which Sequence folder to refer to when looking for the latest information submitted and the latest approved information.

Every CTD Heading where content is provided, and every file should be included in the table.

The table should provide the following information:

- Section
- Heading Title
- Last Sequence where Content was Submitted
- Life Cycle Operation that would have been applied in eCTD format – for example New, Replace or Delete
- Last Sequence where Content was Approved

Table 4 Example Table of Life Cycle Operations

Section	Heading Title	Last Submitted	Life Cycle Operation	Last Approved
1	**Administrative Information and Prescribing Information**			
1.0	Correspondence			
1.0.1	0001 Letter of Application-New Application	0001	New	
1.0.1	0002 Letter of Application-Query Response	0002	New	
1.0.1	0003 Letter of Application-Changes to PI	0003	New	
1.0.1	0004 Letter of Application-Changes to PI	0004	New	

1.0.1	0005 Letter of Application-Additional Strength	0005	New	
1.3	**South African Product Information**			
1.3.1	South African Professional Information			
1.3.1.1	Professional Information (PI)			
1.3.1.1.1	PI - Approved	0004	Replace	0004
1.3.1.1.2	PI - Clean	0004	Replace	0003
1.3.1.1.3	PI - Annotated	0004	Replace	0003
2	**Common Technical Document Summaries**			
2.2	Introduction	0001	New	0001
2.3	Quality Overall Summary			
2.3.1	Introduction	0001	New	0001
2.3.S	Drug Substance - Ibuprofen	0001	New	0001
2.3.P	Drug Product - Tablet	0005	Replace	0001

The complex management of when content was last submitted, and which Sequence contains the content last approved is automatically managed in eCTD. It is one of the major reasons eCTD is the preferred format.

4.5. Life Cycle Operations

Life cycle Operations are not possible in the eSubmission format as it lacks the XML elements to manage and track changes in the Application over time.

The inability to apply Life Cycle Operations reduces the efficiency of the evaluation and is one of the major reasons why eCTDs are the preferred format.

4.6. Files and Folders

4.6.1. File and Folder Naming Conventions

Naming conventions for the content files are part of the Validation Criteria.

- Follow the naming convention provided in the SAHPRA eCTD Validation Criteria
- 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 “-“.
- Always provide evaluator friendly variable components in the file name when multiple files are provided for a section

4.6.2. Folder and File Name – Path Length

The Folder and File Name Path Length requirements are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

4.6.3. Source Documents

The Source Documents requirements are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

5. eCTD Preparation Tools

Information on eCTD Preparation Tools can be found in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

6. Appendix A: Best Practice File Name Variable Component

Important information required for each file is highlighted in Appendix A: Best Practice Leaf Titles of the SAHPRA eCTD Specifications as additional variable information that would be added to the leaf title. Users can utilise the table provided in the SAHPRA eCTD Specifications to get a good idea in many cases how they might be able to differentiate content with the variable file name component.

Some titles include values in brackets – for example [DESCRIPTION]. These help indicate good practice variable components.

7. Appendix B: South African eCTD Granularity Annex

The Granularity Rules are the same as described in the SAHPRA eCTD Specifications. Please refer to the Specifications, same sections, for more information.

8. Change Control

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

- eCTD ECOWAS eSubmission Specification
- eCTD AU Module 1 and Regional Information
- ICH eCTD Specifications v3.2.2

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
- New Functional Requirements
- Experience with Using eSubmissions, 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 SAHPRA eCTD Website.

9. 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.

Date	Version	Description of Change	Effective Date
August 2024	3.1	Updated broken hyperlinks. Removed mention of 2.24 document as it is archived. Comments addressed from industry.	October 2024
June 2024	3.0	Initial version as updated from v1 (which was based on NeeS). Major restructuring of the document and updates to both files required and a new trigger file to collect Envelope information. Most of the content is now referencing the eCTD specifications	July 2024 (with Portal launch)

	v2	Skipped to align versioning with the eCTD 3.0	
July 2019	v1	First publication for implementation	July 2019