South African Health Products
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SAHPRA ECTD SPECIFICATION 3.1 AND GUIDANCE FOR MODULE 1 AND REGIONAL INFORMATION

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration, as well as variations, of medicines in eCTD format. It reflects the current situation and will be regularly updated with changes in legislation and experience gained. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Guidelines and application forms are available from South African Health Products Regulatory Authority website.

Document History

Version	Reason for Amendment	Effective Date
1_23	First publication as working document	February 2013
1	Publication for Implementation of pilot phase and comment	March 2013
2	Amendment of sections Abbreviations & Acronyms, Definitions, 22, 3.1, 4, Appendix 1, Appendix 2 (Table 5), Appendix 3, Appendix 4. Added section 7.6	October 2016
2.1	Correction of DTD, editorial changes	May 2017
2.1	Implementation	May 2017
3	Change from MCC to SAHPRA Amendment of Sections Abbreviations & Acronyms, Definitions, 1 and 4, Appendix 2 & 3 – with immediate effect.	May 2019
3.0	Initial version as updated from 2.1 with major restructuring of the document and updates to both the Envelope and Heading Elements.	April 2024
3.1	Typographical error correction. Addition of definitions for Clones/ Replicas/Duplicates/Line Extensions. Expansion of section 2.2 Initial Sequence to include Baselines	July 2024

	New section added 3.13 Line Extension. 4.3.4.20. Multiple Applications updated to reflect difference of including clones/replicas/duplicates. Inclusion of 2.2.3 Rolling Review. Reference to the schema updated to v3.1 Granularity Annex: typographical correction of 1.2.2.1	
4.0	Transferred to new SAHPRA template	October 2025

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1. Introduction

This document specifies Module 1 and the regional sections 2.3.R/3.2.R of the electronic Common Technical Document (eCTD) for South Africa ("ZA").eCTD is the preferred format for submission to the South African Health Products Regulatory Authority (SAHPRA). eSubmissions will only be accepted by the authority for specified Application types. Please refer to the eSubmission specifications for more information on how to create a ZA eSubmission. eSubmissions are also only planned as a stepping stone to eCTD, they will only be accepted for a limited period of time with the goal to move all CTD based application types to eCTD. Please refer to the roadmap for more detail.

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.

The document should be read in conjunction with the ICH eCTD Specification to prepare a valid eCTD submission for South Africa. The latest version of the ICH eCTD Specification can be found at: http://estri.ich.org/ectd. This eCTD Specification version is based on the ICH eCTD version 3.2.2 Specification.

The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission.

The eCTD specification lists the criteria that will make an eCTD technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority.

Industry to industry, authority to authority and authority to industry transfer is not addressed.

This document contains:

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

Version 3.1 of the Specifications should be read in combination with:

- 2.24 ZA-SAHPRA Guidance for the Submission of the South African CTD / eCTD General and Module 1 and Regional Information version 3.0

- 2.22 ZA-SAHPRA eCTD Validation Criteria version 3.1
- 2.28 ZA-SAHPRA eCTD Q&A Document version 3.0

The eCTD Specifications are designed to assist software vendors and technical staff with understanding the technical setup and creation of a South African eCTD. We encourage regulatory personnel to read and understand the Specifications at a high level and focus on the information provided in:

- Section 2 Business Protocol: Preparing your eCTD Application of this document,
- and Section 3 South African Regional Considerations of this document,
- the 2.24 ZA-SAHPRA Guidance for the Submission of the South African CTD / eCTD General and Module 1 and 2.3.R / 3.2.R,
- sections 2, 4 and 6 of the 2.22 ZA-SAHPRA eCTD Validation Criteria
- and information clarified in the 2.28 ZA-SAHPRA eCTD Q&A Document

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 CTD as defined by the M4 EWG does not cover the full submission that is to be made in a region. It describes only modules 2 to 5, which are common across all regions. The ICH CTD specifies that Module 1 should contain region-specific administrative and product information. The CTD does not describe the content of module 1 because it is regional specific, nor does it describe documents that can be submitted as amendments or variations to the initial application.

The value of producing a specification for the creation of an electronic submission based only upon the modules described in the CTD would be limited. Therefore, the M2 EWG has produced a specification for the eCTD that is applicable to all modules of initial registration applications and for other submissions of information throughout the life cycle of the product, such as variations and amendments.

1.3. 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 South African to also migrate once experience has been obtained by other authorities and a smooth transition can be planned.

1.4. Technical Requirements

The specification is designed to support high-level functional requirements such as the following:

- Copying and pasting
- Viewing and printing of documents
- Annotation of documentation
- Facilitating the exporting of information to databases
- Searching within and across applications
- Navigating throughout the eCTD and its subsequent amendments/variations

1.5. 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 ZA-SAHPRA 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 ID. 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 ID	A unique identifier for an eCTD application. An Application ID must be issued before an eCTD submission can be submitted using the version 3.1 (or higher) specifications. The same Application ID will be used for all Sequences of an eCTD Application and cannot ever be changed.

	The Application ID will also be used as the directory name in the top-level directory. Note for legacy applications, the top-level directory name should continue to be the eCTD identifier used in earlier sequences. The Application ID will be automatically issued by the new SAHPRA Portal.
Application Number	A unique identifier for a product application. Each product (clones, duplicates, strengths) will have a unique application number. The Application Number will remain with the product for its full life cycle and also in archiving, even if it is transferred to a new applicant. The Application Number will be automatically issued by the new SAHPRA Portal.
Authority	Refers to the entity responsible for the evaluation and/or approval of applications for a particular region. In South Africa, this refers to the South African Health Product Regulatory Authority (SAHPRA).
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.
CIPC	The Companies and Intellectual Property Commission (CIPC) is an agency of the Department of Trade, Industry and Competition in South Africa. The CIPC is responsible for the Registration of Companies, Co-operatives and Intellectual Property Rights (trademarks, patents, designs and copyright) and maintenance thereof. The CIPC issues a registration number to all companies which can be used as a unique ID for the company.
CTD	Common Technical Document as defined by ICH and SAHPRA. 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 SAHPRA.
Dossier	Same as Application. See Application for definition.
eCTD	Electronic Common Technical Document – an international electronic standard for the Common Technical Document (CTD) providing the means for transferring information from Applicants to Authorities.
eCTD Application	A collection of electronic documents compiled by an applicant/PHCR in compliance with South African legislation and guidelines in order to seek registration of a medicine, or any amendments thereof. An eCTD Application is also referred to as an Application. See Application for further definition.
eCTD Sequence	See Sequence for definition.
eCTD Submission	See Submission for definition.
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.
Regulatory Activity	Same as Submission. See Submission for definition.
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 Type	The Submission Type describes the type of submission / procedure that the content relates to.
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.
Replica	A replica is defined as a copy of an **already registered** generic product, submitted by the same applicant at any stage during the Master product's life cycle under a different proprietary name and application number as a follow-up sequence of the original registered (Master) product. Thus, the Application ID is the same as the Master's.
Clone	Application submitted by the innovator of an **already registered** NCE, as a copy of its own product under a different proprietary name and application number as a follow-up sequence of the original registered (Master) product, as part of the life cycle of the Master Application. Thus the Application ID is the same as the Master's.
Duplicate	A duplicate application may be for an innovator, a generic or a biosimilar product and is defined as two or more applications submitted simultaneously by the same applicant, which are identical in every aspect except for the proposed proprietary name(s). A duplicate application must be submitted at the same time as the master application. If, for example, an application is submitted days, months or years after the master, it is regarded as not being linked to a master and would follow the normal evaluation process. Internal reliance may however be applied.
Line Extension	Additional products added to the product range are sometimes referred to as 'Line Extensions'. This may include addition of an additional Strengths, Dosage Forms or New Routes of Administration.
Rolling Review	A regulatory tool that is used to speed up the assessment of a promising medicine or vaccine during a public health emergency. Normally, all data on a medicines or vaccine's quality, efficacy and safety and all required documents must be ready at the start of the evaluation in a formal application for marketing authorisation. In the case of a rolling review, the Authority reviews data as it becomes available from ongoing studies.

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.*

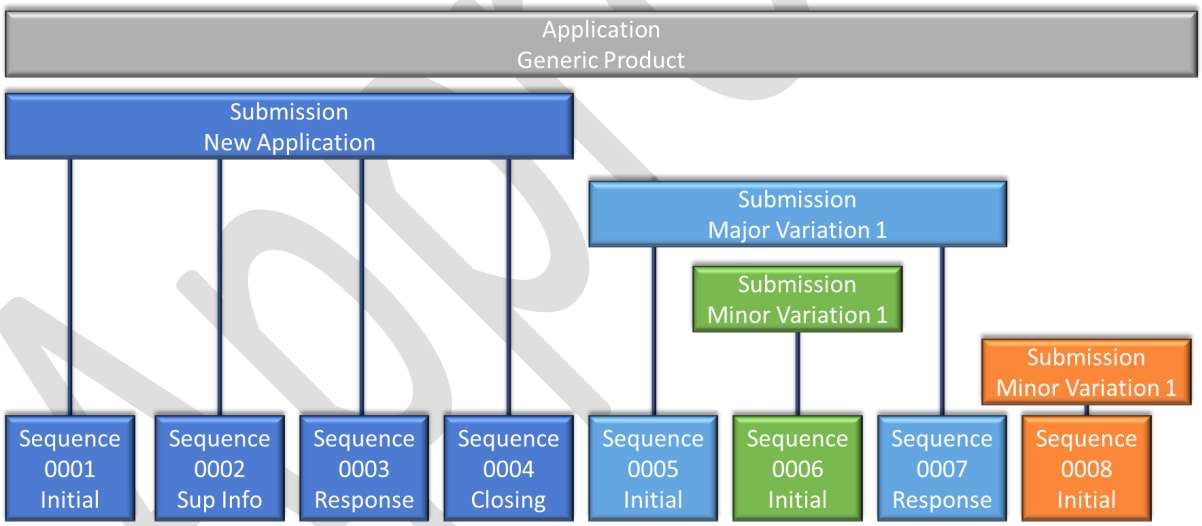

Figure 1: Application, Submission and Sequence Relationship

1.6. Implementation/Transition Plan

For information on the ZA eCTD Specifications version 3.1 implementation, please refer to the 2.26 ZA CTD and ZA eCTD Implementation Roadmap.

2. Business Protocol: Preparing your eCTD Application

2.1. The SAHPRA Application Portal

All Applicants will need to register with the SAHPRA Application Portal. One login will be provided to each Applicant. It is the Applicant's responsibility to manage access using the login ID and password provided. Applicants can change the information associated with the login account as well as change the password when deemed necessary.

The SAHPRA Application Portal will provide critical information required for your eCTD envelope and tracking. It may also in future collect information to produce an electronic Application Form (eAF) or for IDMP purposes (Identification of Medicinal Products).

Applicants should register their Applications and Submissions prior to submitting any related sequences. The portal will provide the following information:

- Application ID
- Application Number(s)
- Submission Number(s)

For more information on the **Portal**, please visit the portal and download the Portal Process Guide or watch the Portal Tutorial.

2.1.1. CIPC Number and Company Name

The company's CIPC Number is required and should be used to identify the Applicant. The SAHPRA Application Portal will store the Applicant's CIPC Number and registered company name. This will be passed on to the evaluation system so it will not be necessary to provide this information in the envelope starting with the eCTD specifications version 3.1.

If two Applicants with different CIPC Numbers were to merge, one of the 2 numbers would be designated for future use.

In the case of Co-applicancy, the CIPC Number of one of the Applicants will be used.

2.1.2. Application ID

The Application ID is a unique identifier for the Application (eCTD or eSubmission) and will be automatically generated for all new applications. For legacy applications, the eCTD identifier previously used as the Application Folder (root node) should be used as Application ID.

Application IDs generated by the Portal will be prefixed with either and “e” for eCTDs or “s” for structured eSubmissions.

For legacy Applications, please continue to use the previous Application Folder name as Application ID and Application Folder for all future Sequences.

2.1.3. The Application Number

An Application Number will be automatically issued for each product, strength, replica/clone/ duplicate by the SAHPRA Application Portal when a new Application is created or a new replica/clone is added to an existing Application.

The Application Number is different depending on the type of product.

- **Orthodox/Biological**: a running 6-digit number e.g., 123456.
- **Complementary**: a running 6-digit number with the prefix “D” e.g., D123456.
- **Veterinary**: a 4-digit number separated by a “/” e.g., 24/06, where the first 2-digits represent the year the application number was requested.
- **Active Pharmaceutical Ingredient Master File** (APIMF) / Drug Master File (DMF): a 4-digit number with the prefix “SAHPRA APIMF”.

An Application Number will be required for:

- Each strength for products with multiple strengths.
- Each replica / clone / duplicate product, also – for example for all strengths of the replica / clone / duplicate.

Multiple Application Numbers can be included in an eCTD Application e.g., it is appropriate to combine different strengths and any replica / clone / duplicate products in a single Application, but different pharmaceutical forms, or schedules should be in separate eCTD Applications.

Table 2 Application Numbers for Different Strengths and Replica / Clone / Duplicates

Product	Strength	Form	Application Number
afriCapsule	200mg	Capsule	123451
afriCapsule HS	100mg	Capsule	123452
afriCapsule DS	400mg	Capsule	123453
genCapsule*	200mg	Capsule	123454
genCapsule* HS	100mg	Capsule	123455
genCapsule* DS	400mg	Capsule	123456

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

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.

2.1.4. The Submission Number

Submission Number will be provided for each new Submission (regulatory activity) e.g., variation, renewal, etc. A single Submission Number will be issued for each submission, even if multiple Application Numbers exist for the eCTD Application.

The Submission Number is made up of a two-digit number representing the year, month, day and minute – **YYMMDDmm**, e.g., 24062634.

Each new Submission in the eCTD will require a new Submission Number. The Application Number will remain the same forever.

If multiple submissions of the same type (e.g. Type IA) are being bundled into the same Submission, multiple submission numbers should be provided, one for each separate Submission.

2.1.5. Uploading Sequences

The SAHPRA Application Portal will be the only valid method for submitting sequences. The upload option will be available in the portal when you select your Application and Submission.

The Portal will validate that the correct Application ID, Application Number(s) and Submission Number(s) have been provided in the Envelope when uploading.

2.2. 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 Splitting the eCTD Application

In the event that a variation would affect one strength or down-schedule one strength resulting in a Line Extension – New Application for that one strength only, a separate eCTD Application may need to be created. For the existing Application, no changes would be required, simply continue on with business as usual but update the Envelope in the next sequence to exclude the Application Number(s) and Proprietary Name(s).

The new Application will need a new Application ID but the existing Application Number(s) should continue to be used. The first Sequence of the new Application should be the next sequential Sequence that would be submitted next in the original eCTD Application. The first Sequence should be Line Extension – New Application and include a Letter of Application explaining why the split in Application was required. A second Sequence should then be submitted as a Baseline Sequence. After that, business as usual can continue.

An eCTD Application cannot be split if there are any open submissions; a withdrawal of all open submissions must be done before an eCTD split is allowed.

Table 8 Scenario for Splitting the eCTD Application

Product A	Product B	Activity/Task
0001		Applicant submits eCTD Application for product with Application Numbers 123456 and 123457.
0002		Applicant submits responses to SAHPRA's queries, and the Application is approved; the product is registered.
0003		Applicant submits a new Submission for a Type II variation with the Sequence Type Initial.
0004		Applicant submits Sequence 0004 to withdraw the Type II variation using the Sequence Type Withdrawal and Related Sequence 0003. The Sequence Description should be "eCTD Application Split".

	0005	Applicant submits a New eCTD Application with Submission Type Line Extension – New Application with a Letter of Application detailing the reason for the split in the eCTD Application (e.g. downscheduling of the one strength).
	0006	Applicant Submits a Baseline Sequence with all approved content from the previous eCTD Application. If open Submissions were withdrawn before the split, these should not be included in the Baseline because these were withdrawn and not approved. Approval of the New Application is given by SAHPRA (possibly after several sequences of responses, etc.).
	0007	Applicant undertakes business as usual in the new eCTD Application.
0005		Applicant undertakes business as usual in the original eCTD Application. If open Submissions were withdrawn, they will need to be resubmitted under a new Submission but files previously submitted should only be referenced, they should not be physically provided again.

If an eCTD Application split and a Transfer of Application are to be performed, the split should be done and completed before the transfer is performed.

Transfer of Application for more information.

2.2.1. Baselines

Use the Submission Type Baseline and Sequence Description "Initial" in the Envelope for the first baseline Sequence.

2.2.2. Ways to Submit a Baseline

The baseline should:

- be submitted as Sequence 0000
- always be a separate Sequence
- only contain previously submitted/approved content
- never include new content

The first new Submission – for example, the next variation – in eCTD format should then be submitted as Sequence 0001.

A Baseline can be submitted as a single initial Submission – Unit, or an iterative approach can be taken in which multiple baseline Sequences are provided over time as and when needed for the review of variations.

2.2.2.1. Baselines Submitted as an Initial eCTD Sequence

It is preferred that a baseline be submitted as a single Sequence and include all the relevant currently valid documents. This eliminates the need to build the baseline overtime and gives the evaluator the best overview of the product for an efficient evaluation process.

Table 3 Single Sequence Approach to a Baseline

Sequence	Submission Type	Sequence Type	Related Sequence
0000	Baseline	Initial	0000
0001	Type IB - Clinical	Initial	0001
0002	Type IB - Clinical	Response	0001
0003	Type II - Proprietary Name Change	Initial	0003
0004	Type II - Safety (Clinical)	Initial	0004

2.2.2.2. Baselines Submitted as Multiple Sequences (Iterative Baseline)

An iterative approach of building a Baseline can be taken if additional time is required to provide Modules 4 and 5. Contact SAHPRA for permission to take this approach. If approved, a deadline to complete the Baseline will be issued and the Applicant will be allowed to submit Sequences up until the deadline as normal as long as the Submissions do not require the content of Modules 4 and 5 for the

evaluation. If the Baseline has not been completed and provided by the deadline, all further non-Baseline Sequences will be rejected in screening until the Baseline is provided.

When creating a baseline Sequence for the first time:

- **Do** add documents previously submitted in the appropriate part of the eCTD structure with the attribute "NEW".
- **Do not** re-submit documents from previous eCTD Sequences.

You can use multiple Sequences to submit a baseline.

Example – one Sequence for the baseline for Modules 1, 2 and 3 followed later by a Sequence for the baseline for Modules 4 and 5.

- **Do** use the Submission Type Baseline in each case.
- **Do** use the Sequence Type Initial on the first baseline Sequence.
- **Do** use the Sequence Type Supplementary Information on each of the baseline Sequences submitted later and indicate the Related Sequence Number of the Initial Sequence.

Make sure the related Sequence for a baseline references itself in the envelope metadata for the Initial Sequence.

Table 4: Multiple Sequence Approach to a Baseline demonstrates how to submit multiple baselines later in the eCTD life cycle.

In this example, the previously submitted content for a variation is submitted as a baseline prior to the initial Sequence for the Submission where it is needed.

These Sequences can be submitted together via an electronic portal or on the same electronic media. Each Sequence should have a cover letter explaining the purpose of the Sequence.
Table 4: Multiple Sequence Approach to a Baseline

Sequence	Submission Type	Sequence Type	Related Sequence
0000	**Baseline**	**Initial**	**0000**
0001	Type II - Safety and Efficacy (Clinical)	Initial	0001
0002	Type IB - Quality	Initial	0002
0003	Type II - Safety and Efficacy (Clinical)	Response	0001
0004	**Baseline**	**Supplementary Information**	**0000**
0005	Type II - Quality	Initial	0005

Mid-Life Cycle Baselines of eCTD Applications

There may be rare circumstances where you may wish to submit a baseline of content previously submitted in the eCTD format. In such cases, you should send an email outlining your proposal to eCTD@sahpra.org.za to discuss the best approach.

A Mid-Life Cycle Baseline should be a collection of all currently approved content of an eCTD where technical issues may hinder further life cycle management of the application. The applicant should copy the Application from the last sequence submitted and create an entirely new Application (not as a new sequence of the existing Application). The sequence number should be the next sequence that would have been submitted in the old application. The other rules for Baselines should be followed and justification should be provided in the Letter of Application along with the SAHPRA contact that provided the permission to provide a Mid-Life Cycle Baseline.

For example: Applicant deleted a complete 3.2.P section, and it is impossible to restore the section OR Applicant did not maintain proper life cycle of several critical documents (attribute "new" instead of "replace"). Applicant can therefore send a request to SAHPRA to submit mid-Life Cycle Baseline.

2.2.3. Rolling Review

A Rolling Review will have a similar life cycle approach as an iterative baseline, however, should have the evaluation pathway as Rolling Review, start as initial sequence 0001 and information should be provided as soon as it becomes available as per the scenario described below.

Table 5: Scenario for a Rolling Review

Sequence	Submission Type	Sequence Type	Related Sequence
0001	New Chemical Entity	Initial	0001
0002	Response Evaluation Query Inspectorate	Response - Inspectorate	0001
0003	New Chemical Entity	Supplementary Information	0001
0004	Response – Evaluation Query Quality	Response - Quality	0001
0005	New Chemical Entity	Supplementary Information	0001

0006	Response – Clinical Evaluation Query	Response – Clinical	0001
Registration			

Rolling Reviews are only applicable in the case of Public Health Emergencies. Kindly refer to the guideline SAHPGL-PEM-01_SAHPGL-PEM-01 _Availability_of_medicines_for_use_in_a_PHE

2.3. Preparing the eCTD Letter of Application

The following new information shall be included in the Letter of Application:

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

  Example: 123456-2412345 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 X version 1.0 and is confirmed to be virus free."

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

    Example: SOFTWARE Y version 2.0 / South Africa 1.0.1 Profile

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

2.4. 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,

  - from other sequences of the same application,
  - from other applications.
- Specifications adhered to
- Details on legacy documents and scanned/OCRed pages
- eCTD Organisation
  - eCTD Attributes
  - 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
- Navigation Aids
  - Hyperlink appearance and strategy
  - Bookmark organisation and strategy, or deviations from recommendations
- List of documents available on request

2.5. eCTD Application Folder Naming Convention

The Application ID should be used also as the name of the Application Folder being used to provide the sequences of the Application.

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

For legacy Applications, please continue to use the previous Application Folder name as Application ID and Application Folder for all future Sequences.

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

Sequences already submitted should not be submitted again.

2.6. 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 ZA-SAHPRA eCTD Validation Criteria.

There are three types of eCTD validation findings:

- **ERROR** – Critical Pass/Fail finding:

- Non-compliance will lead to rejection of the Sequence.
- If errors are unavoidable, contact SAHPRA before submitting the Sequence. Validation findings categorised as errors should be addressed in the Letter of Application 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 Letter of Application.
  - 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 that might be required in the Sequence for the Submission Type declared in the Envelope.
  - Information about Study Tagging Files submitted, etc.
  - Information about content reuse within the same Sequence, from other Sequences in the same Application and from other Applications.

Validate Sequences prior to submitting them to the Authority. SAHPRA may request for a copy of the validation report if issues arise during validation, however; is not required as part of the submission of the Sequence.

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 SAHPRA.

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 warnings.

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

2.7. Submitting your eCTD Sequence(s)

Submit your Sequences via the SAHPRA Application Portal.

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

Feedback on Validation

The Applicant will be notified of the validation results for every 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.

Submitting Parallel Submissions/Sequences

When submitting multiple sequences of the same Application using the SAHPRA Application Portal, the applicant must wait for the validation of the first sequence to be completed with a successful validation result before the next sequence can be submitted. This is to ensure that each sequence or building block of the foundation is secure before additional sequences or pieces are built on top. While validation is pending, the submit option in the portal will be suspended for any Submissions of that same Application.

Submission Tracking

Status fields will be integrated into the portal. As the sequence moves through the evaluation process, status information will be relayed to the portal so that Applicants can stay up to date on the evaluation progress. Status will be provided based on Application, Submission and Overall Sequence as well as the different evaluation units, e.g., Clinical, Quality, Inspectorate, Names and Scheduling, etc.

3. South African 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.

3.1. File Formats

File formats refer to the accepted file type for documents within a Sequence. In most sections, the applicant is required to provide PDF files. 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 6 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 ZA-SAHPRA eCTD Validation Criteria section 6 PDF Analysis.

Table 7: 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.

3.1.1. Module 1

In addition to PDF, as defined by the ICH eCTD Specification Document, 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 Letter of Application.

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.

3.1.2. Module 2 to 5

In addition to the file formats defined for Modules 2 to 5 in the ICH eCTD Specification and the ICH Specifications for Study Tagging Files, we will allow comma separated value (CSV) and plain text (TXT) files in Modules 4 and 5 if appropriate.

3.2. Electronic Signatures

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

- Digital signatures. Please see the Electronic Signature Guidelines Appendices.
- 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.

Please note that all documents uploaded via the portal will be considered as signed and approved by the Applicant. It is therefore very important that Applicants secure their login to the Portal and ensure that only authorised personnel have access to upload and submit sequences.

3.3. Document Navigation Aids

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

3.3.1. 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 Literature References; however individual references should be provided as separate files and uniquely identified.

The Validation Criteria mandates a check of any documents other than 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.

3.3.2. Table of Contents

A Table of Contents (TOC) and/or, if appropriate, a Table of Tables, Table of Figures, etc. can be placed 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.

3.3.3. Document Title Pages

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

3.3.4. 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.

Please note that the validation template may require specific hyperlinks although they are contrary to the rules placed here. It is the intention over time to modify and reduce the requirements for the validation template where reports for information provided can automatically be created.

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 SAHPRA Request will be confirmed according to the Validation Criteria.

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

A report will be created by our validator providing a summary of all hyperlinks and their destinations. This will aid the screening process and ensure that sufficient hyperlinking has been provided from the recommended sections.

Related Information and Guidance

ICH eCTD Specifications – Appendix 7

3.3.5. Document Granularity

For the South African 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 for the appropriate expected granularity. Follow the lowest level of granularity defined for submitting documents.

Note that the M4(R4) Guideline indicates a level of granularity Applicants 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.

Please refer to Appendix B: South African eCTD Granularity Annex for more information on recommended Granularity for Module 1 and 3.2.R.

3.4. Empty or Missing eCTD Sections

Provide detailed statements justifying the absence of expected data or specific CTD sections in the Letter of Application 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 for the Submission Type being submitted.
- Do not submit documents for content marked XE (Excluded: Error) or XW (Excluded: Warning) in the Document Matrix.

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

3.5. 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.

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

We ask Applicants to please strip any larger files associated with the Study Tagging Files were possible. The file size limit for SAHPRA is 200MB. Note that some other authorities allow up to 5GB for XPT files provided in the Study Tagging Files. SAHPRA will not use those files as part of the evaluation and does not want them to be included in the applications. If files are stripped, please address this in the Note to Evaluator and list them under Files Available upon Request.

Related Information and Guidance

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

3.6. Submission of PBRER/PSUR and RMP Reports

Periodic benefit-risk evaluation reports (PBRER) or periodic safety update reports (PSUR) and other risk management plan (RMP) reports (e.g., PV-related safety studies, etc.) 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:
PSUR 2023-06-30 to 2023-12-31;
RMP Report - Phase 3 Study Evaluating the Safety of Product X 2023-01-01

3.7. Updating eCTD Backbone Attributes

3.7.1. Updating ICH Attributes

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

For attributes where changes are more likely to occur – for example, manufacturer in 2.3.P / 3.2.P, a generic variable can be placed in the attribute field e.g., "MNF" and the manufacturer(s) represented by the variable can be declared and maintained in the Note to Evaluator. 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.

A similar approach could be taken for product name in 3.2.P. Since these can never be changed later in the life cycle and proposed names from the initial Sequence of an Application are sometime not accepted, a generic name could be used so not to create confusion over time.

3.7.2. Updating South African Envelope Information

The South African 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.

3.8. Reusing Files

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

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 ID).

When referencing content already used in other locations, a different title can be specified for the content in the new location independent of the title provided in the original location. References are always relative to the location where the XML file is located. For the regional content, that would be the "za" 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., "za" folder.

```
<m1-4-3-clinical>
 <leaf ID="Ne49d5b87f01847d4939baf67cb05a5a8" operation="new"
  xlink:href=
```

```
  "14-expert-information/141-quality/quality-nkosi.pdf"
  checksum="26b84c4ea4c39db30504651bdd7c2b98" checksum-type="MD5">
    <title>1.4.3 Clinical - Dr. A. Nkosi</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 "za", "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/za/14-expert-information/141-quality/quality-ndlovu.pdf"
  checksum="e89f6b9a3824800f531b00a770f3496e" checksum-type="MD5">
    <title>1.4.3 Clinical - Dr. J. Ndlovu</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 "za", "m1", "0002" and Application folders then directing it back down into the "123456" Application folder to the Sequence where the content can be found.

```
<m1-4-3-clinical>
 <leaf ID="N664d6e2d996b4a5b90fc8e2010bbf18a" operation="new"
  xlink:href=
  "../../../../123456/0001/m1/za/14-expert-information/141-quality/quality-toit.pdf"
  checksum="0a7ec7fd25f0627993b120225ca59593" checksum-type="MD5">
    <title>1.4.3 Clinical - Dr. S. du Toit</title>
 </leaf>
</m1-4-3-clinical>
```

Figure 4: Referencing Content used in other Applications

Related Information and Guidance

ICH eCTD Specifications – Appendix 6

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 eCTD:

- Paper
- Other Electronic Files (e.g., eSubmission)

Content from modules 1-5 should be provided.

In Module 1, sequence specific administrative documents e.g., Application Forms, Proof of Payments, Electronic Copy Declarations, etc. do not need to be included.

The first sequence of a Baseline Submission will be 0000 as explained in 2.2 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 the next Sequence (not 0000). Please see 3.12 Transfer of Application for more information.

SAHPRA requires that a baseline submission be provided when switching to eCTD (Submission Type Baseline).

Letter of Application for Baseline Submissions

The purpose of the Baseline Letter of Application is to provide a record of the content used to approve the registration of the product. In addition to the information listed in 2.3 Preparing the eCTD , the following information should be provided in the Letter of Application for Baseline Submissions:

- The format used for the previous submissions (i.e., paper or eSubmission)
- 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 Letter of Applications combined into a single bookmarked document and placed as an annex to the baseline Letter of Application when possible

3.10. 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 ZA-SAHPRA Envelope is designed to allow

Applicants to designate multiple Submission Types in a single Submission. Not all combinations of Submission Types, however, are allowed. Please refer to the Submission Type Matrix to understand which Submission Types can be combined with each other.

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

3.11. Splitting the eCTD Application

In the event that a variation would affect one strength or down-schedule one strength resulting in a Line Extension – New Application for that one strength only, a separate eCTD Application may need to be created. For the existing Application, no changes would be required, simply continue on with business as usual but update the Envelope in the next sequence to exclude the Application Number(s) and Proprietary Name(s).

The new Application will need a new Application ID but the existing Application Number(s) should continue to be used. The first Sequence of the new Application should be the next sequential Sequence that would be submitted next in the original eCTD Application. The first Sequence should be Line Extension – New Application and include a Letter of Application explaining why the split in Application was required. A second Sequence should then be submitted as a Baseline Sequence. After that, business as usual can continue.

An eCTD Application cannot be split if there are any open submissions; a withdrawal of all open submissions must be done before an eCTD split is allowed.

Table 8 Scenario for Splitting the eCTD Application

Product A	Product B	Activity/Task
0001		Applicant submits eCTD Application for product with Application Numbers 123456 and 123457.

0002		Applicant submits responses to SAHPRA's queries, and the Application is approved; the product is registered.
0003		Applicant submits a new Submission for a Type II variation with the Sequence Type Initial.
0004		Applicant submits Sequence 0004 to withdraw the Type II variation using the Sequence Type Withdrawal and Related Sequence 0003. The Sequence Description should be "eCTD Application Split".
	0005	Applicant submits a New eCTD Application with Submission Type Line Extension – New Application with a Letter of Application detailing the reason for the split in the eCTD Application (e.g. downscheduling of the one strength).
	0006	Applicant Submits a Baseline Sequence with all approved content from the previous eCTD Application. If open Submissions were withdrawn before the split, these should not be included in the Baseline because these were withdrawn and not approved. Approval of the New Application is given by SAHPRA (possibly after several sequences of responses, etc.).
	0007	Applicant undertakes business as usual in the new eCTD Application.
0005		Applicant undertakes business as usual in the original eCTD Application. If open Submissions were withdrawn, they will need to be resubmitted under a new Submission but files previously submitted should only be referenced, they should not be physically provided again.

If an eCTD Application split and a Transfer of Application are to be performed, the split should be done and completed before the transfer is performed.

3.12. 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 Relinquishing Applicant should provide withdrawals of any open submissions before providing a Transfer of Application notification. The Sequence Description for the withdrawal should be "Transfer of application". A separate sequence is required for each withdrawal to close each of the individual submissions. Once all open submissions have been closed, The Relinquishing Applicant should provide a Transfer of Application Submission (Submission Type Transfer of Application - Relinquishing).

Then, as the very next sequence, the Acquiring Applicant should provide a Transfer of Application Submission (Submission Type Transfer of Application - Acquiring), stating the Relinquishing Applicant and the eCTD Application ID in the Letter of Application and submitting a copy of the Written Confirmation of Hand-over of Dossier.

No other submission types are allowed between the Submission Type Transfer of Application - Relinquishing and Transfer of Application – Acquiring. These must be submitted one after the other.

Multiple Application Numbers can be combined in a single Application – for example multiple strengths or second brand products. This must be stated in the Letter of Application. 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 Letter of Application in 3.9 Baseline Submissions.
  - The Letter of Application should state the eCTD identifier, the eCTD Application Number(s) and the last Sequence Number provided by the Relinquishing Applicant which included the product now transferred to the Acquiring Applicant and all withdrawals of any open submissions.
- All content provided in the eCTD previously by the Relinquishing Applicant up until the last sequence provided.

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.

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.

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

3.12.1. 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., PSUR, 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 Pharmacovigilance Submission Type. State Transfer of Application in the Sequence Description as the reason for submission.

Once all of the withdrawals and pharmacovigilance information has been provided, the Relinquishing Applicant should:

- Include a Letter of Application
- Provide a Letter of Authorisation confirming the transfer in section 1.2.3.1
  - indicate the Acquiring Applicant and include their CIPC Number
- Submit a Sequence using.
  - Submission Type: Transfer of Application - Relinquishing
  - Sequence Type: Initial

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

3.12.2. Basic Requirements for the Acquiring Applicant

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

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

The new sequence will need to be uploaded to the SAHPRA Application Portal. This will only be possible once the Application has been added in their portal profile. The new product will need to be added to the Applicant's list of products. Please refer to the Portal Tutorial or Portal Guidance for more information.

The Acquiring Applicant should:

- Submit a sequence as the next sequence in the eCTD (do not start the sequence number over with 0001).
- Provide a Baseline as the first sequence if only a partial transfer took place – no baseline is required if all products in the eCTD application were transferred e.g., there was only one product in the eCTD application.
- Include a Letter of Application confirming the transfer and indicate the Application ID of the previous Application.
- Letter of Authorisation and Written Confirmation of Handover of Dossier (i.e., receipt of the entire eCTD as submitted to SAHPRA to date) should be provided in section 1.2.3.2.
- Submit a Sequence using:
  - Submission Type: Transfer of Application - Acquiring
  - Sequence Type: Initial

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

3.12.3. Order of Events for Transfer of Application

- Relinquishing Applicant
  - Withdraw any open submissions
  - Provide any relevant pharmacovigilance information
  - Submit a Transfer of Application – Relinquishing
- Acquiring Applicant
  - Submit a Transfer of Application – Acquiring as next sequence in the eCTD. This must be the very next sequence after the Transfer of Application Relinquishing

- Submit Baseline sequence if applicable
- Submit any new Submissions and business as usual

No other submission types are allowed between the Submission Type Transfer of Application - Acquiring and Transfer of Application – Acquiring. These must be submitted one after the other.

3.12.4. Scenarios for Transfer of Application

3.12.4.1. Simple Transfer of Application

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

Table 9: Simple Transfer of Application

Applicant ABC	Applicant XYZ	Activity/Task
0001		Applicant ABC submits eCTD Application for product with Application Number 123456
0002		Applicant ABC submits responses to SAHPRA's queries and the Application is approved; the product is registered.
0003		Applicant ABC provides a Submission Pharmacovigilance with Sequence Description "Transfer of Application".
0004		Applicant ABC initiates the transfer of the product to Applicant XYZ by submitting a Submission Transfer of Application – Relinquishing. Applicant ABC provides the eCTD for Application Numb er 123456 (Sequences 0001-0004) to Applicant XYZ.
	0005	Applicant XYZ submits Submission Transfer of Application - Acquiring to confirm the transfer using Submission Number 123456. The transfer of the product from Applicant ABC to Applicant XYZ is approved by SAHPRA.
	0006	Applicant XYZ undertakes business as usual.

3.12.4.2. 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 10: 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 123456.
0002		Applicant ABC submits responses to SAHPRA's queries, and the Application is approved; the product is registered.
0003		Applicant ABC submits a new Submission for a Type II Variation with the Sequence Type Initial.
0004		Applicant ABC submits Sequence 0004 to withdraw the Type II Variation using the Sequence Type Withdrawal and Related Sequence 0003. The Sequence Description should be "Transfer of Application".
0005		Applicant ABC provides a Submission Pharmacovigilance with Sequence Description "Transfer of Application".
0006		Applicant ABC initiates the transfer of the product to Applicant XYZ by submitting a Submission Transfer of Application – Relinquishing. Applicant ABC provides the eCTD for Application Number 123456 (Sequences 0001-0006) to Applicant XYZ.
	0007	Applicant XYZ submits Submission Transfer of Application - Acquiring to confirm the transfer using Submission Number 123456. The transfer of the product from Applicant ABC to Applicant XYZ is approved by SAHPRA.
	0008	Applicant XYZ undertakes business as usual.

3.12.4.3. 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 11 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 123456 and 123457. The Application folder "cacdbbciajaa" is used as issued by the Application Portal.
0002		Applicant ABC submits responses to SAHPRA's queries and the Application is approved; products are registered.
0003		Applicant ABC provides a Submission Pharmacovigilance with Sequence Description "Transfer of Application".
0004		Applicant ABC initiates the transfer of the product 123456 to Applicant XYZ but not 123457 to Applicant XYZ by submitting a Submission Transfer of Application – Relinquishing. Applicant ABC provides the eCTD for Application ID "cacdbbciajaa1" (Sequences 0001-0004) to Applicant XYZ.
	SAHPRA Application Portal	A new application is created in the Application Portal for product 123456 and the Application ID "caceabcjbddb" is issued.
	0005	Applicant XYZ submits Submission Transfer of Application - Acquiring to confirm the transfer using Application Number 123456. The Application folder "caceabcjbddb" is used as issued by the Application Portal. The transfer of the product from Applicant ABC to Applicant XYZ is approved by SAHPRA. (Approval may only be issued once the expected following Baseline Submission is provided.
	0006	Applicant XYZ submits Submission Baseline to representing the current view of the application 123456 (Sequences 0001-0004). The Sequence Description "Transfer of Application" should be provided.
	0007	Applicant XYZ undertakes business as usual.
0005		Applicant ABC undertakes business as usual but only lists Application Number 123457 in the Envelope.

The Application Folder continues to be “cacdbbciajaa”.

3.13. Line extensions

In the event that a variation would affect one strength or down-schedule one strength resulting in a Line Extension – New Application for that one strength only, a separate eCTD Application would need to be created. Please refer to sections 2.2 Initial Sequence and 3.11 Splitting the eCTD Application.

Line extensions for a new route of administration or a new indication should have the submission type Line Extension – New Application, submitted as an initial sequence (0001) with its own application ID and application Number.

In the event, that a new strength is added (Line Extension – New Strength) or a new dosage form is introduced (Line Extension – New Dosage Form), these applications fundamentally alter the terms of the initial registration and thus cannot be evaluated according to a variation’s procedure. Extension applications will typically be accompanied by a new registration certificate. In terms of procedure, extension applications will be treated as new registrations by SAHPRA.

Line Extension – New Strength: submissions can be submitted as part of an existing application, as the next sequence. New application number and Proprietary names should be added to the envelope section

Line Extension – New Dosage Form should be submitted as a new application with their own Application ID and Application Number – as sequence 0001, as this is considered a “new product”.

4. South African Module 1 General Architecture

4.1. Backbone File for South Africa Module 1

The South African Module 1 eCTD backbone file is comprised of:

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

4.1.1. Creating the Module 1 eCTD backbone file

To create the South African 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 using authenticated eCTD preparation software.
2. Create the Envelope Elements containing the appropriate metadata values describing the Application, Submission, Sequence, Multiple Application and Contact details.
3. Create content as needed for the Sequence:
    a. Module 1 Heading Elements – organising the South African Module 1 in accordance with the Specifications.
    b. Leaf Element – reference to each file being submitted along with other information such as eCTD checksum and life cycle information.
4. Name the South African Module 1 eCTD backbone file za-regional.xml and place it in the za 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.

4.1.2. Stylesheets

In addition to the ICH standard style sheet, the South African Module 1 is also provided with a standard stylesheet. You must submit eCTD Applications with the stylesheet.

Existence of the stylesheet is checked during the validation process.

4.1.3. Optional HTML File

An HTML rendition of the ICH and/or regional backbone can be provided. If provided, the renditions must have been created using the style sheets provided in the "util" folder and must be placed beside the corresponding backbone file.

HTML renditions can be used to:

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

The HTML renditions of the backbone files cannot be referenced in the backbone files.

4.2. XML Root Element

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

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

The line breaks inside of the za-sahpra_ectd Element as shown in the following excerpt are not mandatory.

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

<za-sahpra_ectd schema-version="3.1"
                xmlns="za-sahpra_ectd"
                xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
                xsi:schemaLocation="za-sahpra_ectd ../../util/dtd/za-regional.xsd"
                xmlns:xlink="http://www.w3.org/1999/xlink" >
```

Figure 5: XML Root Element

4.3. Envelope Elements

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

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

- **Application** – High level Application information valid for multiple if not all Submissions.
- **Submission** – Information relating to the Submission (regulatory activity) that is being submitted.
- **Sequence** – Information relating to the Sequence that is being submitted.
- **Multiple Applications** – Information on additional Applications (products) e.g., replicas/clones/duplicates included in the eCTD Application are listed with Application Number and Product Name.
- **Contact Details** – Information on who should be contacted should questions arise during the validation 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 4.3.3 The Defined Lists.

In comparison to earlier versions, information about the Applicant is no longer provided via the Envelope. This information including the CIPC Number, Applicant's Registered Name, and the User ID of the user that uploaded the sequence to the portal will all be provided by the Portal to the evaluation system.

4.3.1. Envelope Overview

Table 12 Overview of the Envelope Elements

Element	Description	Constraint	Occurrence	Defined List
za-envelope	Root element for envelope meta-data	Mandatory	Single	
application	Parent element for Application meta-data indicating Type	Mandatory	Single	X
application-id	Application Identifier	Mandatory	Single	
application-number	Application Number(s) (Master Application if Multiple Products)	Mandatory	Unique	
proprietary-name	Proprietary Name(s)	Mandatory	Unique	
dosage-form	Dosage Form	Mandatory	Single	
inn	International Non-proprietary Names	Mandatory	Unique	
apimf-number	APIMF Number	Optional	Unique	
pmf-number	PMF Number	Optional	Unique	
vamf-number	VAMF Number	Optional	Unique	
smf-number	Site Master File Number	Mandatory	Unique	
submission	Parent element for Submission meta-data indicating Type	Mandatory	Unique	X
evaluation-path	Evaluation Pathway	Mandatory	Single	X
submission-lead	The SAHPRA program responsible for the submission evaluation	Mandatory	Single	X
submission-number	Submission Number	Mandatory	Unique	
sequence	Parent element for Sequence meta-data	Mandatory	Single	
sequence-type	Sequence Type	Mandatory	Unique	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	
multiple-applications	Multiple Application Indicator of any replicas/clones/duplicates with required value for "proprietary-names" giving the Proprietary Name and "application-numbers" giving the Application Number for each additional Application.	Optional	Multiple	
contact	Parent element for Contact meta-data indicating Type	Mandatory	Multiple	X
contact-name	Contact Name	Mandatory	Single	
contact-email	Contact Email	Mandatory	Single	

3

4.3.2. Submitting Multiple Values in the Envelope

Please provide a separate Element for each entry when submitting multiple values for Envelope Elements where multiple or unique constraints are applied:

- Application Number
- Proprietary Name
- INN
- APIMF Number
- PMF Number
- VAMF Number
- SMF Number
- Submission Type
- Submission Number
- Sequence Type
- Multiple Applications, and
- Contact Type.

```
<za-envelope>
    <application code-version="1.0" code="app-type-1">
        <application-id>cacdbbciajaa1</application-id>
        <application-number>580023</application-number>
        <application-number>580024</application-number>
        <application-number>580025</application-number>
        <proprietary-name>afriCapsule Forte 400mg/50mg</proprietary-name>
        <proprietary-name>afriCapsule 200mg/50mg</proprietary-name>
        <proprietary-name>afriCapsule HD 100mg/50mg</proprietary-name>
        <dosage-form>Capsule</dosage-form>
        <inn>ibuprofen</inn>
        <inn>codeine</inn>
        <apimf-number>0001-D</apimf-number>
        <apimf-number>0002-D</apimf-number>
        <pmf-number>PMF0041/2021</pmf-number>
        <pmf-number>PMF0023/2019</pmf-number>
        <vamf-number>VAMF0056/2020</vamf-number>
        <vamf-number>VAMF0106/2021</vamf-number>
        <smf-number>V071</smf-number>
        <smf-number>L102</smf-number>
        <smf-number>S083</smf-number>
    </application>
    <submission code-version="1.0" code="sub-type-15">
        <evaluation-path code-version="1.0" code="evaluation-path-1"/>
        <submission-lead code-version="1.0" code="submission-lead-4"/>
        <submission-number>24123451</submission-number>
        <submission-number>24123452</submission-number>
        <submission-number>24123453</submission-number>
    </submission>
    <submission code-version="1.0" code="sub-type-17">
```

```
        <evaluation-path code-version="1.0" code="evaluation-path-1"/>
        <submission-lead code-version="1.0" code="submission-lead-4"/>
        <submission-number>24123454</submission-number>
        <submission-number>24123455</submission-number>
        <submission-number>24123456</submission-number>
    </submission>
    <sequence>
        <sequence-type code-version="1.0" code="seq-type-3"/>
        <sequence-type code-version="1.0" code="seq-type-4"/>
        <sequence-description>Change of Address of Applicant</sequence-description>
        <sequence-date>2024-03-06</sequence-date>
        <sequence-number>0010</sequence-number>
        <related-sequence-number>0010</related-sequence-number>
    </sequence>
    <multiple-applications proprietary-names="ABC" application-numbers="123454.1"/>
    <multiple-applications proprietary-names="LMN" application-numbers="123455.2"/>
    <multiple-applications proprietary-names="XYZ" application-numbers="123456.3"/>
    <contact code-version="1.0" code="contact-type-1">
        <contact-name>Dr. Portia Chabalala</contact-name>
        <contact-email>portia.chabalala@pharma-inc.co.za</contact-email>
    </contact>
    <contact code-version="1.0" code="contact-type-3">
        <contact-name>Johan Van Der Merwe</contact-name>
        <contact-email>johan.vdmerwwe@pharma-inc.co.za</contact-email>
    </contact>
</za-envelope>
```

Figure 6: Sample Code for Submitting Multiple Values in the Envelope

4.3.3. The Defined Lists

The defined lists are separate XML files maintained by SAHPRA 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).

The version numbers will be changed to the next major version any time a new code is added or retired. A minor version will be created if there are any changes to the value's descriptions.

```
<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 SAHPRA 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 za-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 SAHPRA 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 – Official defined list for the South African eCTD Elements

4.3.4. Envelope Attributes

4.3.4.1. Application Type

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

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 – Official defined list for Application Type

4.3.4.2. Application ID

An identifier provided by the SAHPRA Application Portal when a new Application is created.

It is a 14-character identifier and is unique when generated by the Portal.

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

Legacy Applications

Please note that for legacy applications where eCTD sequences have already been submitted, the Root Folder will continue to be used as the Application ID.

We will be assigning all applicants with new Application IDs that are independent of the Application Numbers. Once assigned, only the new Application ID should be used.

All applications should be submitted in a root folder named after the Application ID.

Example: caceabdaajcbdf

```
<application-id>caceabdaajcbdf</application-id>
```

Figure 10 Envelope Element: Application Identifier

4.3.4.3. Application Number

If an eCTD Application has multiple product Applications, e.g. clones / duplicates, one of the products must be selected as the "Master Product". Only the Application Numbers for the "Master Product" should be included under Application Number.

Enter the Application Number(s) assigned to the master product including all strengths if multiple strengths are part of the application.

Do not include the Application Number(s) for any of the clones / duplicates as they will need to be listed separately under Multiple Applications.

See 2.1.3 The Application Number for more information on Application Numbers.

Example (Orthodox): 123456

Example (Complementary): D123456

Example (Veterinary): 24/06

Example (APIMF): SAHPRA APIMF 1234

```
<application-number>123456</application-number>
```

Figure 11 Envelope Element: Application Number

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

4.3.4.4. Proprietary Name(s)

The name as proposed or registered.

For API Master Files, insert drug substance name and APIMF holder name.

Example: afriCapsule

Example: amoxicillin AfriPharma

```
<proprietary-name>afriCapsule</proprietary-name>
```

Figure 12 Envelope Element: Proprietary Names

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

4.3.4.5. Dosage Form

The official Dosage Form should be provided in all lower-case.

Example: capsule

```
<dosage-form>capsule</dosage-form>
```

Figure 13 Envelope Element: Dosage Form

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

The recognised International Non-proprietary Name should be given for the active ingredients and pharmaceutical drug if available. It should be written in all lower-case letters and provided exactly as officially listed in international lists e.g., WHO INN, British Approved Names (BAN), United States Pharmacopoeia (USP), etc. without abbreviations.

Example: amoxicillin

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

Figure 14 Envelope Element: INN

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

4.3.4.7. APIMF Number

If a APIMF is referenced in the eCTD application, the APIMF Number as issued should be added.

```
<apimf-number>1234</apimf-number>
```

Figure 15 Envelope Element: APIMF Number

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

4.3.4.8. PMF Number

If a Plasma Master File (PMF) is reference in the eCTD application, the PMF Number as issued should be added. Please note that a corresponding

```
<pmf-number>PMF0003/2023</pmf-number>
```

Figure 16 Envelope Element: PMF Number

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

4.3.4.9. VAMF Number

If a Vaccine Master File (VAMF) is reference in the eCTD application, the VAMF Number as issued should be added.

```
<vamf-number>VAMF0123/2022</vamf-number>
```

Figure 17 Envelope Element: VAMF Number

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

4.3.4.10. SMF Number

The Site Master File (SMF) Number for all manufacturers referenced in the eCTD application should be added as issued.

```
<smf-number>S001/4567V014</smf-number>
```

Figure 18 Envelope Element: SMF Number

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

4.3.4.11. Submission Type

The Submission Element section contains all the Submission related information for the regulatory activity 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.

The Submission Type must be indicated for the Submission Element indicating the type of regulatory activities being undertaken with the Submission.

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, withdrawals and/or closing) should only list the Submissions that are directly affected by the content being submitted in the follow-up Sequence. For example, if a Type IA Quality Submission and a Type IB Quality Submission are combined in the first Sequence, but a response was only required for the Type IB Quality, the Type IA Quality Submission Type 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 – Official defined list for Submission Type
- Submission Type Matrix – A summary of the allowed combinations of Submission Types in a single Sequence.

4.3.4.12. Evaluation Pathway

The Evaluation Pathway applicable to the Submission being submitted should be indicated.

Example: eval-path-1

```
<evaluation-path> code-version="1.0" code="eval-path-1" </evaluation-path>
```

Figure 20 Envelope Element: Evaluation Pathway

Related Information and Guidance

- evaluation-path – Official defined list for Evaluation Pathway

4.3.4.13. Submission Lead

The Submission Lead applicable to the Submission being submitted should be indicated.

Example: sub-lead-1

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

Figure 21 Envelope Element: Submission Lead

Related Information and Guidance

- submission-lead – Official defined list for Submission Lead

4.3.4.14. Submission Number(s)

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

See 2.1.4 The Submission Number for more information on Submission Numbers.

If appropriate, multiple Submission Numbers can be given for a particular Submission e.g., if you are bundling multiple of the same activity (assuming the Submission Type Matrix allows the combination).

Example: 24123451

```
<submission-number>24123451</submission-number>
```

Figure 22 Envelope Element: Submission Number

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

4.3.4.15. 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 however multiple types of Responses can be specified as types. Responses can only be combined with other responses.

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

*** Please refer to the list online for the types of responses available and valid e.g.,**

- Response - Clinical
- Response - Quality
- Response - Inspectorate
- Response - N&S

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

Figure 23 Envelope Element: Sequence Type

Related Information and Guidance

- sequence-type – Official defined list for Sequence Type

4.3.4.16. 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 Letter of Application 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: New Application

Example: Response to 2021-11-20 LOQ

Example: Indication Psoriasis to be added

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

Figure 24 Envelope Element: Sequence Description

4.3.4.17. 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 Letter of Application and in the Application Form but does 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.

The Sequence Date should be formatted YYYY-MM-DD.

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 Letter of Application.

Example: 2025-03-06

```
<sequence-date>2025-03-06</sequence-date>
```

Figure 25 Envelope Element: Sequence Date

4.3.4.18. Sequence Number

Four-digit number matching the Sequence folder being submitted.

New Applications should start with the Sequence 0001.

Legacy Applications should first submit a Baseline Submission which 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>0011</sequence-number>
```

Figure 26 Envelope Element: Sequence Number

4.3.4.19. Related Sequence Number

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

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 13 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**	Type II Variation	Initial
0005	**0005**	Type 1b Variation	Initial
0006	**0006**	Type 1a Variation	Initial
0007	**0004**	Type II Variation	Supplementary Information
0008	**0004**	Type II Variation	Response
0009	**0004**	Type II Variation	Response
0010	**0006**	Type 1a Variation	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 and the Related Sequence Number in the AU regional specifications 3.1, the ECOWAS regional specifications 1.0 and the SG regional specifications 1.0.

Example: 0001

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

Figure 27 Envelope Element: Related Sequence Number

4.3.4.20. Multiple Applications

Any duplicates should be submitted with the master application at the same time as the initial sequence (0001). Replicas / clones should be submitted with the Master Application as next sequential sequence of a Master Application. The master application proprietary name and application numbers should be provided in the envelope elements described in sections 4.3.4.3 and 4.3.4.4. The additional application numbers and proprietary names of the replicas / clones / duplicates should be provided under Multiple Submissions.

Note that if a transfer of application is done or a cancellation of a registered product and limited to just an application that was listed under Multiple Submissions section, it should be removed and no longer listed in any future sequences submitted. If additional replicas / clones / duplicates are added to the eCTD Application, please add them to this section.

For more information on how to handle multiple product applications bundled into one eCTD Application, please refer to the 2.40 Guidance Multiple Submission of the Same Application for Registration with Different Proprietary Names.

Example: Application Number: 123454 | Proprietary Name: ABC Pill

```
<multiple-applications proprietary-names="ABC Pill" application-numbers="123454"/>
```

Figure 28 Envelope Element: Multiple Applications

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

Related Information and Guidance

- 2.40 Guidance Multiple Submission of the Same Application for Registration with Different Proprietary Names

4.3.4.21. 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. At least one Local Applicant contact must be provided.

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 29 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 – Official defined list for Contact Type

4.3.4.22. Contact Name

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

Example: Dr. Sipho Ndlovu

```
<contact-name>Dr. Sipho Ndlovu</contact-name>
```

Figure 30 Envelope Element: Contact Name

4.3.4.23. Contact Email

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

Example: sipho.ndlovu@pharma-inc.co.za

```
<contact-email>sipho.ndlovu@pharma-inc.co.za</contact-email>
```

Figure 31 Envelope Element: Contact Email

4.4. Heading and Leaf Elements

4.4.1. Module 1 Heading Elements

The sections list the Heading Elements of the South African eCTD Module 1 v3.1 which should be provided in the <m1-za> element.

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

- Please refer to the 2.24 ZA-SAHPRA Guidance for the Submission of the South African CTD / eCTD General and Module 1 and 2.3.R / 3.2.R version 3.0 and SAHPRA eCTD website for the expected information under each of these sections. Please note that some sections may not be mandatory. We encourage to regularly check for updates to the Document Matrix.

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

4.4.1.1. 1.0 Correspondence

Table 14 Heading Elements 1.0 - Correspondence

Section ID	Title	XML-Element
1.0	**Correspondence**	**m1-0-application-letter**
1.0.1	Letter of Application	m1-0-1-application-letter
1.0.2	Note to Evaluator	m1-0-2-note-to-evaluator
1.0.3	Correspondence with SAHPRA	m1-0-3-correspondence-from-authority
1.0.4	Response to Input Request	m1-0-4-response-to-authority
1.0.5	Meeting Information	m1-0-5-meeting-info

4.4.1.2. 1.2 Administrative Information

Table 15 Heading Elements 1.2 - Administrative Information

Section ID	Title	XML-Element
1.2	**Administrative Information**	**m1-2-application**
1.2.1	Application Form	m1-2-1-application-form
1.2.2	**Annexes**	**m1-2-2-annexes**
1.2.2.1	Proof of Payment	m1-2-2-1-proof-of-payment
1.2.2.2	Letter of Authorisation	m1-2-2-2-letter-of-authorisation
1.2.2.3	Dossier Product Batch Information	m1-2-2-3-dossier-product-batch-information
1.2.2.4	Electronic Copy Declaration	m1-2-2-4-electronic-copy-declaration
1.2.2.5	Curriculum Vitae of the Person Responsible for Pharmacovigilance	m1-2-2-5-cv-pharmacovigilance
1.2.2.6	API Change Control	m1-2-2-6-api-change-control
1.2.2.7	EMA Certificate for a Vaccine Antigen Master File (VAMF)	m1-2-2-7-vamf-certificate
1.2.2.8	EMA Certificate for a Plasma Master File (PMF)	m1-2-2-8-pmf-certificate
1.2.2.9	Declaration of Sameness for Replicas and Clones	m1-2-2-9-declaration-sameness
1.2.2.10	Letter of Permission from HCR for Replica	m1-2-2-10-letter-permission-hcr
1.2.2.A	Additional Annexes	m1-2-2-a-additional-annexes
1.2.3	**Change in Applicant**	**m1-2-3-change-in-applicant**
1.2.3.1	Letter of Authorisation from Product Owner to New Registrant	m1-2-3-1-loa-from-prod-owner
1.2.3.2	Written Confirmation of Hand-over of Dossier	m1-2-3-2-confirmation-of-hand-over
1.2.4	Patent Declaration	m1-2-4-patent-declaration
1.2.5	Checklists, Validation Templates	m1-2-5-checklists-val-templates
1.2.A	Additional Administrative Information	m1-2-a-additional-admin-info

4.4.1.3. 1.3 South African Product Information

Table 16 Heading Element 1.3 - South African Product Information

Section ID	Title	XML-Element
1.3	**South African Product Information**	**m1-3-za-labelling-packaging**
1.3.1	**South African Professional Information**	**m1-3-1-sapi**
1.3.1.1	**Professional Information (PI)**	**m1-3-1-1-pi**
1.3.1.1.1	PI - Approved	m1-3-1-1-1-pi-approved
1.3.1.1.2	PI - Clean	m1-3-1-1-2-pi-clean
1.3.1.1.3	PI - Annotated	m1-3-1-1-3-pi-annotated
1.3.1.2	**Standard References**	**m1-3-1-2-stdrefs**
1.3.1.2.1	Reference Product - Local	m1-3-1-2-1-ref-prod-local
1.3.1.2.2	Other References	m1-3-1-2-2-other-refs
1.3.2	**Patient Information Leaflet (PIL)**	**m1-3-2-pil**
1.3.2.1	PIL - Approved	m1-3-2-1-pil-approved
1.3.2.2	PIL - Clean	m1-3-2-2-pil-clean
1.3.2.3	PIL - Annotated	m1-3-2-3-pil-annotated
1.3.3	**Labels**	**m1-3-3-labels**
1.3.3.1	Labels - Approved	m1-3-3-1-labels-approved
1.3.3.2	Labels - Clean	m1-3-3-2-labels-clean
1.3.3.3	Labels - Annotated	m1-3-3-3-labels-annotated
1.3.4	Braille	m1-3-4-braille
1.3.5	Foreign Prescribing and Patient Information	m1-3-5-foreign-prescribing-pat-info
1.3.6	**Artwork and Samples**	**m1-3-6-artwork-samples**
1.3.6.1	Statement Confirming Submission of Samples	m1-3-6-1-statement-of-samples
1.3.6.2	Artwork and Pictures of Samples	m1-3-6-2-artwork-pics-of-samples
1.3.6.3	Batch Manufacturing Record of the Sample	m1-3-6-3-batch-of-samples
1.3.6.4	CoA of the Sample	m1-3-6-4-coa-samples

4.4.1.4. 1.4 Information about the Experts

Table 17 Heading Elements 1.4 - Information about the Experts

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

4.4.1.5. 1.5 Specific Requirements for different Types of Applications

Table 18 Heading Elements 1.5 - Specific Requirements for different Types of Applications

Section ID	Title	XML-Element
1.5	**Specific Requirements for different Types of Applications**	**m1-5-specific-requirements**
1.5.1	Literature Based Submissions	m1-5-1-literature-based
1.5.2	**Amendments/Variations**	**m1-5-2-amendment**
1.5.2.1	Tabulated Schedule of Amendments	m1-5-2-1-amendment-schedule
1.5.2.2	**Medicines Register Details**	**m1-5-2-2-medicine-register**
1.5.2.2.1	Medicines Register Details	m1-5-2-2-1-medicine-register
1.5.2.2.2	Registration Certificates	m1-5-2-2-2-registration-certificates
1.5.2.3	Affidavit by Responsible Pharmacist	m1-5-2-3-affidavit
1.5.3	Proprietary Name Applications and Changes	m1-5-3-proprietary-name
1.5.4	Genetically Modified Organisms	m1-5-4-gmo
1.5.6	Bioequivalence Trial Information	m1-5-6-btif
1.5.6.1	Generic Applications (BTIF)	m1-5-6-1-btif
1.5.6.2	Biowaiver	m1-5-6-2-biowaiver
1.5.7	Abridged Applications (Abridged/Verified Review Document)	m1-5-7-abridged-apps

Section ID	Title	XML-Element
1.5.A	Additional Types of Applications Specific Requirements	m1-5-a-additional-types-applications

Note 1: 1.5.5 – PI and PIL amendments/updates – Moved to 1.3.1.1 and 1.3.2

4.4.1.6. 1.6 Environmental Risk Assessment

Table 19 Heading Elements 1.6 - Environmental Risk Assessment

Section ID	Title	XML-Element
1.6	**Environmental Risk Assessment**	**m1-6-environ-risk-assessment**
1.6.1	Non-GMO (Genetically Modified Organisms)	m1-6-1-nongmo
1.6.2	GMO (Genetically Modified Organisms)	m1-6-2-gmo

4.4.1.7. 1.7 Good Manufacturing Practice

Table 20 Heading Elements 1.7 - Good Manufacturing Practice

Section ID	Title	XML-Element
1.7	**Good Manufacturing Practice**	**m1-7-gmp**
1.7.1	Date of Last Inspection of each Site	m1-7-1-last-inspection
1.7.2	Inspection Reports or Equivalent Document	m1-7-2-inspection-report-or-equivalent
1.7.3	Latest GMP Certificate or a Copy of the Appropriate Licence	m1-7-3-gmp-certificate
1.7.4	**Release**	**m1-7-4-release**
1.7.4.1	API	m1-7-4-1-api
1.7.4.2	IPIs	m1-7-4-2-ipi
1.7.4.3	Finished Product Release Control (FPRC) Tests	m1-7-4-3-fprc-tests
1.7.4.4	Finished Product Release Responsibility (FPRR) Criteria	m1-7-4-3-fprr-criteria

Section ID	Title	XML-Element
1.7.5	Confirmation of Contract	m1-7-5-contract-confirmation
1.7.7	SAPC Registration	m1-7-7-sapc-reg
1.7.8	Registration with Registrar of Companies	m1-7-8-comp-reg
1.7.9	Other Documents Relating to the Applicant/PHCR	m1-7-9-docs-phcr
1.7.11	Manufacturing Permits	m1-7-11-manufacturing-permit
1.7.12	Inspection Flow Diagram	m1-7-12-inspection-flow-diagram
1.7.13	Organogram	m1-7-13-organogram
1.7.14	PQR	m1-7-14-pqr
1.7.A	Additional GMP Documents	m1-7-a-additional-gmp-documents

Note 2:

- 1.7.6 – CPP (WHO Certification Scheme) – Moved to 1.10.6
- 1.7.10 – Sample and Documents – Moved to 1.3.6
- 1.7.10.1 – Confirmation of submission of sample – Moved to 1.3.6.1
- 1.7.10.2 – Batch manufacturing record of the sample – Moved to 1.3.6.3
- 1.7.10.3 – CoA of the sample – Moved to 1.3.6.4

4.4.1.8. 1.8 Information Relating to Pharmacovigilance

Table 21 Heading Elements 1.8 - Information Relating to Pharmacovigilance

Section ID	Title	XML-Element
1.8	**Information Relating to Pharmacovigilance**	**m1-8-info-relating-pv**
1.8.1	Pharmacovigilance Systems	m1-8-1-pv-systems
1.8.2	Risk Management Plan	m1-8-2-risk-management-plan

Note 3: 1.8 – Details of Compliance with Screening Outcomes – Moved to 1.2.5

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.

4.4.1.9. 1.9 Individual Patient Data – Statement of Availability

Table 22 Heading Elements 1.9 - Individual Patient Data - Statement of Availability

Section ID	Title	XML-Element
1.9	**Individual Patient Data - Statement of Availability**	**m1-9-indiv-patient-data**

4.4.1.10. 1.10 Foreign Regulatory Status

Table 23 Heading Elements 1.10 - Foreign Regulatory Status

Section ID	Title	XML-Element
1.10	**Foreign Regulatory Status**	**m1-10-foreign-reg-status**
1.10.1	Tabulated List of Foreign Regulatory Status	m1-10-1-countries-same-appl
1.10.2	Registration Certificate or Marketing Authorisation	m1-10-2-foreign-reg-certif-or-ma
1.10.4	**Data Set Similarities**	**m1-10-4-data-set-similarities**
1.10.4.1	Data Set Similarities	m1-10-4-1-data-set-similarities
1.10.4.2	Declaration of Sameness	m1-10-4-2-declaration-sameness
1.10.5	RRA Reports	m1-10-5-rra-reports
1.10.6	CPP (WHO certification scheme)	m1-10-6-cpp

Note 4: 1.10.3 – Foreign Prescribing and Patient Information – Moved to 1.3.5

4.4.1.11. 1.11 Bioequivalence Trial Information (Removed)

This section is no longer valid in the specification version 3.1 and should not be used.

Content should now be submitted under section 1.5.6.

4.4.1.12. 1.12 Paediatric Development Programme

Table 24 Heading Elements 1.12 - Paediatric Development Programme

Section ID	Title	XML-Element
1.12	Paediatric Development Programme	m1-12-paediatric-dev-program

4.4.1.13. 1.13 Risk Management Plan (Removed)

This section is no longer valid in the specification version 3.1 and should not be used.

Content should now be submitted under 1.8.2.

4.4.1.14. 1.A Additional Data

Table 25 Heading Elements 1.A - Additional Data

Section ID	Title	XML-Element
1.A	Additional Data	m1-a-additional-data

Please use node extensions with titles that begin with the sequence number and a description when using the Additional Data section. All content should be addressed either in the cover letter or response document with a reason why the content is being provided in the Additional Data section. Please see 4.4.3 Node Extensions.

4.4.1.15. Discontinued or Redefined Elements

The structure of the South African Module 1 has been modified and updated to be more in line and harmonised with other regions. This means that several sections have been added but also moved or removed. Some elements have been elevated to a structural element status with additional sub-elements. This means content is no longer allowed at those locations where it was previously submitted and the use of the lifecycle operation 'New' or 'Replace' will result in a validation Error. The validation criterion 4.5.4 allows for an exemption so that the life cycle operation 'Delete' can be used to remove content from the sections that have been moved, removed, or redefined as a structural element. If a replace is required in any of these sections, please delete the document in the old location and provide the new version as 'New" in the new location. Please address this in the Note to Reviewer and/or Letter of Application.

Table 26 Discontinued or Redefined Elements

Section ID	Title	XML-Element	Moved to
1.0	Correspondence	m1-0-application-letter	New Structural Element
1.3.1.2	Standard References	m1-3-1-2-stdrefs	New Structural Element
1.3.2	Patient Information Leaflet (PIL)	m1-3-2-pil	New Structural Element
1.3.3	Labels	m1-3-3-labels	New Structural Element
1.5.5	PI and PIL amendments/updates	m1-5-5-pi-amendment	1.3.1.1 and 1.3.2
1.7.6	CPP (WHO Certification Scheme)	m1-7-6-cpp	1.10.6
1.7.10.1	Sample and Documents	m1-10-sample-documents	1.3.6.1
1.7.10.2	Confirmation of submission of sample	m1-7-10-1-sample-submission-confirmation	1.3.6.3
1.7.10.3	CoA of the sample	m1-7-10-2-sample-bmr	1.3.6.4

Section ID	Title	XML-Element	Moved to
1.8	Details of Compliance with Screening Outcomes	m1-8-compliance-screening	1.2.5
1.10.3	Foreign Prescribing and Patient Information	m1-10-3-foreign-pi	1.3.5
1.10.4	Data Set Similarities	m1-10-4-data-set-similarities	New Structural Element
1.11	Bioequivalence Trial Information	m1-11-be-trial-info	1.5.6
1.13	Risk Management Plan	m1-13-risk-management-plan	1.8.2

4.4.2. Leaf Element

The leaf elements provide the content for each heading element.

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

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

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

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

Figure 32: Leaf Element Explained

Each leaf element contains the following attributes when appropriate:

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

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

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

4.4.3. Node Extensions

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

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

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

General Rules for Using Node Extensions:

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

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

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

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

- Nest the node extensions but make sure the first node extension is at the lowest level in the eCTD structure.

  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.

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
  Example: additional data provided in 1.A

You should use the node-extension elements:

- for all clinical studies and content provided in Module 5.3

Note that if node extensions are not used for clinical studies, 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 are not the lowest level of the eCTD Structure

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

4.4.4. Regional Information 2.3.R / 3.2.R

The general structure of the Regional Information is as follows:

R Regional Information
R.1 Pharmaceutical and Biological availability
R.1.1 Overview
R.1.2 Reference product/s (local and foreign)
R.1.3 Certificates of Analysis
R.1.4 Pharmaceutical availability studies
R.2 Parent API Manufacturer with various sites
R.3 Certificates of suitability with respect to the Ph.Eur. (CEPs)
R.4 Multiple API manufacturers
R.5 Medical devices
R.6 Materials of animal and-or human origin
R.7 Batch records of samples
R.8 Other

All fields are optional and only submitted where applicable.

4.4.4.1. 2.3.R Regional Information Summary

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

4.4.4.2. 3.2.R Regional Information

Leaf elements in 3.2.R Regional Information heading 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 Pharmaceutical and Biological Availability.

Any Additional Regional Information required or requested by SAHPRA should be provided as leaves in the 3.2.R.8 Other node extension. Each document should be provided separately and should have a Leaf Title clearly identifying the content.

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

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

4.5. Life Cycle Operations

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

- New
- Replace
- Delete
- Append

We encourage you to:

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

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

4.5.1. Specific Life Cycle Operations

The nodes with specific life cycle operations mandated for a South African eCTD are summarised in Table 27: Nodes with Specific Life Cycle Operations. Adherence to these specific requirements will be validated.

Table 27: Nodes with Specific Life Cycle Operations

Section	Title	Life Cycle Operation	Validation Severity
1.0.1	Letter of Application	New	Error
1.0.3	Correspondence from SAHPRA	New	Error
1.0.4	Response to SAHPRA Request	New	Error
1.2.1	Application Form	New	Error

Section	Title	Life Cycle Operation	Validation Severity
1.2.2.1	Proof of Payment	New	Error
1.2.2.4	Electronic Copy Declaration	New	Error
1.3.1.1*	Professional Information	Replace**	Warning***
1.3.1.2.1	Reference Product - Local	Replace**	Warning***
1.3.2*	Patient Information Leaflet	Replace**	Warning***
1.3.3*	Labels	Replace**	Warning***
1.3.5	Foreign Prescribing and Patient Information	Replace**	Warning***
1.3.6.2	Artwork and Pictures of Samples	Replace**	Warning***
1.3.6.3	Batch Manufacturing Record of the Sample	Replace**	Warning***
1.3.6.4	CoA of the Sample	Replace**	Warning***
1.5.2.1	Tabulated Schedule of Amendments	New	Error
1.7.1	Date of Last Inspection of each Site	Replace**	Warning***
1.7.3	Latest GMP Certificate or a Copy of the Appropriate Licence	Replace**	Warning***
1.7.5	Confirmation of Contract	Replace**	Warning***
1.7.7	SAPC Registration	Replace**	Warning***
1.7.12	Inspection Flow Diagram	Replace**	Warning***
1.7.13	Organogram	Replace**	Warning***
1.8.2	Risk Management Plan	Replace**	Warning***
1.10.1	Tabulated List of Foreign Regulatory Status	Replace**	Warning***

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

** 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.

*** Provide explanation in the Letter of Application as to why a Replace was not possible.

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 section and an annotated copy of the proposals should be placed in the Annotated section. The current Approved Product Information from an earlier Sequence will be visible so there is no need to resubmit the Approved Product Information.

Once proposed changes presented in Clean 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 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.

4.5.2. 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.

4.5.2.1. *Application Withdrawal*

Application withdrawal indicates a total withdrawal of the product from the South African market. In the case of a APIMF, withdrawal is only possible once the APIMF 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 Letter of Application should be included as “New” and explain why the eCTD Application is being withdrawn.
- No further content or life cycle is required.

4.5.2.2. *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 Letter of Application 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.

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

4.5.2.3. 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.

4.5.3. Life Cycle Operations for Rejected Submissions

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

4.5.3.1. Rejected Submissions and Work Grouping

If 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.

4.6. Files and Folders

4.6.1. File and Folder Naming Conventions

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

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

- Ensure all content is referenced by the appropriate XML files for efficient navigation.
- Provide precise but informative Leaf Titles to aid evaluators.
- Ensure the basic construction of the eCTD is maintained.
- Adhere to the basic ICH eCTD rules for folder and file names:
  - Use alphanumeric lower-case characters only – for example a-z & 0-9.
  - Do not use spaces.
  - Do not use any special characters other than hyphen "-".
- Adhere to the naming conventions for leaf titles as described in Table 28: Minimum Naming Conventions Matrix.

If a file naming convention is sought for technical purposes, the file names previously defined in earlier specifications can be used as these will be used for any eSubmissions moving forward. For new sections, please refer to the latest eSubmission specifications for guidance. File names beyond what is specified in Table 28: Minimum Naming Conventions Matrix are not required but could be used as a best practice recommendation where necessary by solutions.

Table 28: Minimum Naming Conventions Matrix

Folders	Files	Description
cacdbbciajaa		Application folder representing the Application ID
0001		Sequence folder with four-digit number e.g., 0001
m1		Content folder for Module 1 Documents in Accordance with ICH
za		South African Country Specific Folder
	za-regional.xml	South African 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] Folder in Accordance with ICH
	ich-ectd-3-2.dtd	ICH DTD for Modules 2 to 5
	xlink.xsd	W3C schema for Xlink 1.1 (referenced from za-regional.xsd)
	xml.xsd	W3C schema for XML namespace (referenced from za-regional.xsd)
	za-regional.xsd	South African Regional Backbone schema for Module 1
style		Style Sheet Folder in Accordance with ICH
	ectd-2-0.xsl	ICH Style-sheet for Modules 2 to 5
	za-regional.xsl	South African Style-sheet for Module 1
index.xml		Index file in accordance with ICH
index-md5.txt		MD5 checksum in accordance with ICH

4.6.2. 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.

[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 like a DTD, but also allows for the definition of datatypes for elements and attributes and allows support for namespaces, whereas a DTD does not.

4.6.3. 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 29: Source File Requirements

Requirement	Requirement Details
1.2.5 Checklist – Validation Template	MS Word File in addition to the PDF
1.3.1.1 Professional Information (PI)	MS Word File in addition to the PDF
1.3.2 Patient Information Leaflet (PIL)	MS Word File in addition to the PDF
1.3.3 Labels	MS Word File in addition to the PDF
1.5.6 Generic Applications (BTIF)	MS Word File in addition to the PDF
1.5.7 Abridged Applications	MS Word File in addition to the PDF
3.2.R.8 QOS	MS Word File in addition to the PDF
3.2.R.8 QIS	MS Word File in addition to the PDF
3.2.R.8 SCORE	MS Word File in addition to the PDF

5. eCTD Preparation Tools

SAHPRA 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 ZA eCTD will be able to provide an Application compatible with any solution SAHPRA has chosen to use for evaluation.

It is important to note that the evaluation tool used by an Authority should in no way influence the solution selected by an Applicant. Any eCTD created by any eCTD Tool that conforms to South African requirements will work with any eCTD evaluation solution that also conforms to the South African 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

  - Cost and Level of Functionality
- Find a solution which supports current and ongoing South African 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 South African eCTD requirements.
- minimises the possibility of technical validation errors which can cause delays in the overall regulatory process.

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.

Applicants 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.

6. Appendix A: Best Practice Leaf Title Recommendations

Table 30: Best Practice Leaf Title Recommendations

Section	Best Practice Leaf Title
1.0	**Correspondence**
1.0.1	[SEQUENCE] Letter of Application [DESCRIPTION]
1.0.2	[SEQUENCE] Note to Evaluator
1.0.3	Correspondence [DATE] [DESCRIPTION]
1.0.4	Response [DATE OF CORRESPONDENCE FROM SAHPRA] [DESCRIPTION]
1.0.5	Meeting Information [DESCRIPTION]
1.2	**Application**
1.2.1	[SEQUENCE] App Form [PRODUCT] [STRENGTH] [DESCRIPTION]
1.2.2	**Annexes**
1.2.2.1	[SEQUENCE] Proof of Payment [DESCRIPTION]
1.2.2.2	Letter of Authorisation [DESCRIPTION]
1.2.2.3	Dossier Product Batch Information [DESCRIPTION]
1.2.2.4	[SEQUENCE] Electronic Copy Declaration [DESCRIPTION]
1.2.2.5	Curriculum Vitae of the Person Responsible for Pharmacovigilance [DESCRIPTION]
1.2.2.6	API Change Control [DESCRIPTION]
1.2.2.7	EMA Certificate for a Vaccine Antigen Master File (VAMF) [DESCRIPTION]
1.2.2.8	EMA Certificate for a Plasma Master File (PMF) [DESCRIPTION]
1.2.2.9	Declaration of Sameness for Replicas and Clones [DESCRIPTION]
1.2.2.10	Letter of Permission from HCR for Replica [REPLICANAME]
1.2.2.A	Additional Annexes [DESCRIPTION]
1.2.3	**Change in Applicant**
1.2.3.1	Letter of Authorisation from Product Owner to New Registrant [APPLICANT]
1.2.3.2	Written Confirmation of Hand-over of Dossier [APPLICANT]
1.2.4	Patent Declaration

Section	Best Practice Leaf Title
1.2.5	[SEQUENCE] Validation Templates
1.2.A	[DESCRIPTION]
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 [DATE]
1.3.1.1.2	PI - Clean
1.3.1.1.3	PI - Annotated
1.3.1.2	**Standard References**
1.3.1.2.1	Reference Product – Local [PRODUCTNAME]
1.3.1.2.2	Other References
1.3.2	**Patient Information Leaflet (PIL)**
1.3.2.1	PIL - Approved [DATE]
1.3.2.2	PIL - Clean
1.3.2.3	PIL - Annotated
1.3.3	**Labels**
1.3.3.1	Labels - Approved [DATE]
1.3.3.2	Labels - Clean
1.3.3.3	Labels - Annotated
1.3.4	**Braille**
1.3.5	**Foreign Prescribing and Patient Information**
1.3.6	**Artwork and Samples**
1.3.6.1	Statement Confirming Submission of Samples
1.3.6.2	Artwork and Pictures of Samples
1.3.6.3	Batch Manufacturing Record of the Sample
1.3.6.4	CoA of the Sample
1.4	**Information about the Experts**
1.4.1	Quality
1.4.2	Nonclinical
1.4.3	Clinical
1.5	**Specific Requirements for different Types of Applications**
1.5.1	Literature Based Submissions
1.5.2	**Amendments/Variations**
1.5.2.1	Tabulated Schedule of Amendments
1.5.2.2	**Medicines Register Details**
1.5.2.2.1	Medicines Register Details
1.5.2.2.2	Registration Certificates
1.5.2.3	Affidavit by Responsible Pharmacist
1.5.3	Proprietary Name Applications and Changes
1.5.4	Genetically Modified Organisms
1.5	**Generic Applications (BTIF)**
1.5.6.1	Generic Applications (BTIF)
1.5.6.2	Biowaiver
1.5.7	Abridged Applications (Abridged/Verified Review Document)

Section	Best Practice Leaf Title
1.5.A	[TYPEOFAPPLICATION] [DESCRIPTION]
1.6	**Environmental Risk Assessment**
1.6.1	Non-GMO (Genetically Modified Organisms)
1.6.2	GMO (Genetically Modified Organisms)
1.7	**Good Manufacturing Practice**
1.7.1	Date of Last Inspection of each Site
1.7.2	Inspection Reports or Equivalent Document
1.7.3	Latest GMP Certificate or a Copy of the Appropriate Licence [NAME OF MANUFACTURER/FPRC/FPRR/API SUPPLIER]
1.7.4	**Release**
1.7.4.1	API
1.7.4.2	IPIs
1.7.4.3	Finished Product Release Control (FPRC) Tests
1.7.4.4	Finished Product Release Responsibility (FPRR) Criteria
1.7.5	Confirmation of Contract
1.7.7	SAPC Registration
1.7.8	Registration with Registrar of Companies
1.7.9	Other Documents Relating to the Applicant/PHCR
1.7.11	Manufacturing Permits
1.7.12	Inspection Flow Diagram
1.7.13	Organogram
1.7.14	PQR
1.7.A	GMP Document [DESCRIPTION]
1.8	Information Relating to Pharmacovigilance
1.8.1	Pharmacovigilance Systems
1.8.2	Risk Management Plan
1.9	**Individual Patient Data - Statement of Availability**
1.10	**Foreign Regulatory Status**
1.10.1	Tabulated List of Foreign Regulatory Status
1.10.2	Registration Certificate or Marketing Authorisation
1.10.4	**Data Set Similarities**
1.10.4.1	Data Set Similarities
1.10.4.2	Declaration of Sameness
1.10.5	RRA Reports
1.10.6	CPP (WHO certification scheme)
1.12	**Paediatric Development Programme**
1.12	[DESCRIPTION]
1.A	**Additional Data**
1.A	[DESCRIPTION]
2	**Summaries and Overviews**
2.2	Introduction
2.3	**Quality Overall Summary**
2.3.S	Drug Substance [SUBSTANCE] [MANUFACTURER]
2.3.P	Drug Product [MANUFACTURER] [DOSAGE]

Section	Best Practice Leaf Title
2.3.A	Appendices
2.3.R	Regional Information
2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	**Nonclinical Written and Tabulated Summaries**
2.6.1	Introduction
2.6.2	Pharmacology Written Summary
2.6.3	Pharmacology Tabulated Summary
2.6.4	Pharmacokinetics Written Summary
2.6.5	Pharmacokinetics Tabulated Summary
2.6.6	Toxicology Written Summary
2.6.7	Toxicology Tabulated Summary
2.7	**Clinical Summary**
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods
2.7.2	Summary of Clinical Pharmacology Studies
2.7.3	Summary of Clinical Efficacy
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]

Section	Best Practice Leaf Title
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
3.2.P.4	**Control of Excipients**
3.2.P.4.1	Compendial Excipients
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical Procedures
3.2.P.4.3	Validation of Analytical Procedures
3.2.P.4.4	Justification of Specifications
3.2.P.4.5	Excipients of Human or Animal Origin
3.2.P.4.6	Novel Excipients
3.2.P.5	**Control of Drug Product**
3.2.P.5.0	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]

Section	Best Practice Leaf Title
3.2.R	**Regional Information**
3.2.R.1	**Pharmaceutical and Biological availability**
3.2.R.1.1	Overview
3.2.R.1.2	Reference Product [PRODUCTNAME]
3.2.R.1.3	CoA [DESCRIPTION]
3.2.R.1.4	Pharmaceutical Availability Study [STUDYNUMBER]
3.2.R.2	Parten API Manufacturer with Various Site [MANUFACTURER]
3.2.R.3	CEP [SUBSTANCE] [MANUFACTURER]
3.2.R.3	CPQ [SUBSTANCE] [MANUFACTURER]
3.2.R.3	SAHPRA APIMF Approval Letter [SUBSTANCE] [MANUFACTURER]
3.2.R.4	Multiple API Manufacturers [SUBSTANCE] [MANUFACTURER]
3.2.R.5	Medical Device [DEVICENAME]or[DEVICEDESCRIPTION]
3.2.R.6	Materials of Animal or Human Origin [MATERIAL]
3.2.R.7	Batch Records of Samples [BATCHNUMBER]
3.2.R.8	[DESCRIPTION]
3.2.R.8	SCORE
3.2.R.8	QOS
3.2.R.8	QIS
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]

Section	Best Practice Leaf Title
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]

Section	Best Practice Leaf Title
5.4	[AUTHORS(S), DATE] e.g., Smith, 2018

7. Appendix B: South African eCTD Granularity Annex

The following granularity should be observed when submitting the regional content to the ZA-SAHPRA.

Content not Allowed	A comprehensive file is not appropriate
TOC	TOC Node - not used in eCTD, possible use in eSubmissions
ONE File	One comprehensive file should be created for these sections
MULTIPLE Files	Multiple files can be provided if appropriate
**	Both PDF and Source File e.g., MS Word should be provided

Module 1 ZA	1.0	1.0.1		
		1.0.2		
		1.0.3		
		1.0.4		
		1.0.5		
	1.1			
	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	
			1.2.2.6	
			1.2.2.7	
			1.2.2.8	
			1.2.2.9	
			1.2.2.10	
			1.2.2.A	
		1.2.3	1.2.3.1	
			1.2.3.2	
		1.2.4		
		1.2.5**		
		1.2.A		
	1.3	1.3.1		
			1.3.1.1	1.3.1.1.1**
				1.3.1.1.2**
				1.3.1.1.3**
			1.3.1.2	1.3.1.2.1
				1.3.1.2.2
		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		
		1.3.5		
		1.3.6	1.3.6.1	

			1.3.6.2	
			1.3.6.3	
			1.3.6.4	
	1.4	1.4.1		
		1.4.2		
		1.4.3		
	1.5	1.5.1		
		1.5.2		
			1.5.2.1	
			1.5.2.2	1.5.2.2.1
				1.5.2.2.2
			1.5.2.3	
		1.5.3		
		1.5.4		
		1.5.6	1.5.6.1**	
			1.5.6.2**	
		1.5.7**		
		1.5.A		
	1.6	1.6.1		
		1.6.2		
	1.7	1.7.1		
		1.7.2		
		1.7.3		
		1.7.4	1.7.4.1	
			1.7.4.2	
			1.7.4.3	
			1.7.4.4	
		1.7.5		
		1.7.7		
		1.7.8		
		1.7.9		
		1.7.11		
		1.7.12		
		1.7.13		
		1.7.14		
		1.7.A		
	1.8	1.8.1		
		1.8.2		
	1.9			
	1.10	1.10.1		
		1.10.2		
		1.10.4		
			1.10.4.1	
		1.10.5	1.10.4.2	
		1.10.6		
	1.12			
	1.A			

8. Change Control

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

- SG-HSA eCTD Specification and Guidance for Module 1 and Regional Information
- eCTD ECOWAS Module 1 and Regional Information
- eCTD AU Module 1 and Regional Information
- EU Module 1 eCTD Specification
- GCC Module 1 eCTD Specification
- The eCTD Backbone Files Specification for US Module 1
- 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 SAHPRA | Electronic Common Technical Document (ECTD) Submissions.

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
July 2024	3.1 Jul24	Typographical error correction. Addition of definitions for Clones / Replicas / Duplicates / Line Extensions. Expansion of section 2.2 Initial Sequence to include Baselines New section added 3.13 Line Extension. 4.3.4.20. Multiple Applications updated to reflect difference of including clones / replicas / duplicates. Inclusion of 2.2.3 Rolling Review. Reference to the schema updated to v3.1 Granularity Annex: typographical correction of 1.2.2.1	July 2024
March 2024	3.0 Apr24	Initial version as updated from 2.1 with major restructuring of the document and updates to both the Envelope and Heading Elements.	April 2024
May 2019	3 May19	Change from MCC to SAHPRA Amendment of Sections Abbreviations & Acronyms, Definitions, 1 and 4, Appendix 2 & 3 – with immediate effect.	May 2019
May 2017	2.1 Nov16	Implementation	May 2017
Sep 2016	2.1 Nov16	Correction of DTD, editorial changes	May 2017
Sep 2016	2 Oct16	Amendment of sections Abbreviations & Acronyms, Definitions, 22, 3.1, 4, Appendix 1, Appendix 2 (Table 5), Appendix 3, Appendix 4. Added section 7.6	
Mar 2013	1	Publication for Implementation of pilot phase and comment	Mar 2013
Feb 2013	1_23	First publication as working document	Feb 2013