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Global eCTD Regulatory Updates

South Africa SAHPRA eCTD v3.1

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www.ennov.com | contact-us@ennov.com | +1 (833) 366-6887

The Electronic Common Technical Document (eCTD) has become the global standard and has long been the backbone of regulatory submissions, streamlining the process of dossier submissions for marketing authorization applications. As the landscape of life sciences continues to evolve, so too does the eCTD standard.

The transition to eCTD continues to be a significant step towards digital transformation in the regulatory landscape.

Global eCTD regulatory changes are updates, modifications, or new requirements implemented by different regulatory authorities which affect how pharmaceutical companies prepare, submit, and manage eCTD dossiers These changes can impact various aspects of the eCTD lifecycle, including the structure of the dossier, the types of information required, electronic publishing processes, and submission and review procedures.

Key global eCTD regulatory changes include:

- **Harmonization:** Efforts are ongoing to harmonize eCTD requirements across different regions to simplify the submission process for pharmaceutical companies operating globally.
- **Version Updates:** The eCTD specification itself undergoes periodic updates (e.g., from eCTD v3.2.2 to v4.0) to accommodate new types of data and to improve the efficiency of the submission process.
- **Regional Specificities:** Despite harmonization efforts, each region (e.g., Europe, the United States, Japan, and other parts of the world) may have specific requirements or modules within the eCTD that are unique to their regulatory processes.
- **Implementation Deadlines:** Health authorities often provide transition periods and deadlines for companies to adapt to new eCTD requirements. It is crucial for companies to stay informed and prepare for these changes in advance.
- **Training and Tools:** As eCTD requirements evolve, companies must invest in training for their staff and may need to update their electronic submission tools and systems to comply with the latest standards.
- **Lifecycle Management:** Changes may also affect how post-approval changes and lifecycle management of products are handled within the eCTD framework.
- **Quality Control:** Ensuring the accuracy and completeness of eCTD submissions is critical. Regulatory changes may introduce new quality control measures or expectations
- **Communication:** Health authorities typically communicate eCTD regulatory changes through guidance documents, webinars, workshops, and other outreach efforts to help industry stakeholders understand and comply with the new requirements.

South African Health Products Regulatory Authority (SAHPRA) eCTD v3.1

Currently, South African Health Products Regulatory Authority (SAHPRA) uses the eCTD v2.1 submission format. Starting in October 2024, SAHPRA will require the eCTD v3.1 submission format technological interdependencies associated with a variation change control and submission.

The key features of South Africa eCTD Specifications v3.1 are:

The SAHPRA Application Portal	Discontinued or Redefined Elements
Envelope	Specific Life Cycle Operations
Specifications	

The SAHPRA Portal

The SAHPRA Application Portal is the online platform used by SAHPRA. It has been created to streamline the application process, making it more efficient and transparent. It also provides a centralized location for applicants to track the progress of their submissions and communicate with SAHPRA regarding their applications.

Portal functions include:

- **Application ID:** A unique identifier for the Application (eCTD or eSubmission) will be generated automatically for all new applications.
- **Application Number(s):** Application Number(s) 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. Application Numbers will be different depending on the type of product.
- **Submission Number:** A submission number will be assigned for each new Submission. A Submission is defined as a regulatory activity, such as a variation, renewal etc.
- **CIPC Number and Company Name:** The Applicant's CIPC number and registered company name. This will be passed on to the evaluation system, so that it will not be necessary to provide this information in the envelope.
- **Portal Trigger File:** A file that is uploaded to SAHPRA's submission portal to signal the beginning of a submission process or to alert the system that a new submission is ready for review. This is mandatory for all sequences starting 1 April 2024.
- **Uploading Sequences:** This is the only valid method for submitting sequences.
- **Submission Tracking:** The status of the evaluation. This will be provided for the Application and Submission, allowing applicants to stay up to date on the evaluation progress.

Customer Stakeholder Portal

An online interface that provides access to important information, resources, and services related to customer and stakeholder interactions. It often includes features like dashboards, document repositories, communication tools, and support systems.

- **Centralised Access:** The portal centralizes information and services, making it easier for stakeholders to access.
- **Enhanced Engagement:** Direct access to essential information and interactive elements promotes greater engagement and collaboration.
- **Efficency Gains:** Automate standard processes and provide self-service options to reduce the manual process.
- **Data Insights**
- **Scalability:** Provides a foundation for future digital transformation initiatives.
- **Transaparency and Accountability:** Access real-time information and tracking tools.
- **Improved Communication:** The portal has the potential to acquire useful data on stakeholder interactions and preferences. Analyzing this data helps understanding requests from stakeholders, improving service delivery, and making knowledgeable choices.

SAHPRA Envelope Structure

The new Envelope Structure is categorized into 3 elements:
The tables below show elements that have been ~~deleted~~ in v3.1, retained from v2.0 and newly added in v3.1.

APPLICATION ELEMENT

v2.0	v3.1
~~Applicant~~	
	Application (Type)
	Application ID
Application Number	Application Number (s)
Proprietary Name	Proprietary Name (s)
Dosage Form	Dosage Form
INN	INN
	APIMF Number
	PMF Number
	VAMF Number
	SMF Number

SUBMISSION ELEMENT

v2.0	v3.1
~~Submission~~	
Submission Type	Submission Type
~~Submission Efficacy Description~~	
	Evaluation Pathway
	Submission Lead
	Submission Number

SEQUENCE ELEMENT

v2.0	v3.1
	Sequence
	Sequence Type
	Sequence Description
	Sequence Date
eCTD Sequence Number	Sequence Number
Related eCTD Sequence Number	Related Sequence Number
Multiple Applications	Multiple Applications
Proprietary Names	Proprietary Names
Application Numbers	Application Numbers
	Contact Name
	Contact Name
	Contact Email

SPECIFICATIONS

- Electronic Common Technical Document Specifications are according to the ICH M2 EWG eCTD Specification V 3.2.2.
- The acceptable formats for document submission are PDF and MS Word (rtf).
- Working Documents are not acceptable in v3.1
- Source File Requirements: Following sections require MS Word File in addition to the PDF -

Section ID	Title
1.2.5	Checklist – Validation Template
1.3.1.1	Professional Information (PI)
1.3.2	Patient Information Leaflet (PIL)
1.3.3	Labels
1.5.6	Generic Applications (BTIF)
1.5.7	Abridged Applications
3.2.R.8	QOS
3.2.R.8	QIS
3.2.R.8	SCORE

DISCONTINUED OR REDEFINED ELEMENTS

The structure of the South African Module has been modified to harmonise with other regions. This means that several sections have been added, moved, or removed.

Section ID	Title	Moved to
1	Correspondence	New Structural Element - Changed to Parent-element
1.3.1.2	Standard References	New Structural Element - Moved to Sub-element
1.3.2	Patient Information Leaflet (PIL)	New Structural Element
1.3.3	Labels	New Structural Element
1.5.5	PI and PIL amendments/updates	Moved to 1.3.1.1 and 1.3.2
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
1.8	Details of Compliance with Screening Outcomes	Moved to 1.2.5
1.10.3	Foreign Prescribing and Patient Information	Moved to 1.3.5
1.10.4	Data Set Similarities	New Structural Element
1.11	Bioequivalence Trial Information	Removed Content should now be submitted under section 1.5.6
1.13	Risk Management Plan	Removed Content should now be submitted under section 1.8.2

Specific Life Cycle Operations

Sections that have been redefined in v3.1 only exist in the new location. Content is no longer allowed in the old locations and the documents cannot be used to perform any lifecycle operations. Documents must be deleted in v2.1 and placed in the redefined structure as "new."

Specific Life Cycle Operations are applicable to the following section:

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
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.

Overview of New Validation Structure

SAHPRA has replaced the outdated 21-part validation criteria with a more streamlined six-part structure that is already utilized by various regulatory agencies, featuring logical groupings of requirements.

Part 1 - eCTD XML Identification	**Part 4 -** South African regional backbone requirements
Part 2 - Files and Folders	**Part 5 -** Study Tagging File backbone requirements
Part 3 - ICH backbone requirements	**Part 6 -** PDF Analysis

In July 2024, The South African Health Products Regulatory Authority (SAHPRA) has introduced an updated electronic Common Technical Document (eCTD) v3.1 specification, introducing several updates and enhancements to the regulatory submission process with related to the version 3.0. These changes are designed to streamline submissions, improve clarity, and ensure that the eCTD format remains aligned with the evolving needs of the pharmaceutical industry.

One of the initial improvements in the eCTD v3.1 is the correction of typographical errors. These corrections ensure that the document is free from minor errors that could cause confusion or misinterpretation. Accuracy is paramount in regulatory submissions, and SAHPRA's attention to detail in correcting these errors underscores the importance of clear and precise communication in the eCTD format. It is anticipated that there will be an additional cosmetic update to version 3.1.1 of the electronic Common Technical Document (eCTD) specification. This update is expected to be minor in nature and will not result in any changes to the underlying schema or regional files. The focus of this update is likely to be on improving the aesthetics or user experience without altering the technical aspects of the eCTD submission process.

DEFINITIONS FOR CLONES, REPLICAS, DUPLICATES, AND LINE EXTENSIONS:

SAHPRA has added clear definitions for clones, replicas, duplicates, and line extensions in the eCTD v3.1 specification. These definitions provide sponsors with a better understanding of how to manage and submit variations of their dossiers. Clones, replicas, and duplicates refer to different methods of creating similar submissions, while line extensions pertain to adding new indications or formulations to an existing product. These definitions help standardize the submission process and facilitate a more efficient review by SAHPRA.

EXPANSION OF SECTION 2.2 INITIAL SEQUENCE TO INCLUDE BASELINES:

The eCTD v3.1 has expanded the scope of Section 2.2 to include baselines in the initial sequence. This expansion reflects the importance of establishing a solid foundation for subsequent submissions. The baseline submission serves as the initial comprehensive dossier, and this update ensures that sponsors understand the critical elements required for a complete and compliant initial sequence. 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.

The baseline should:

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

There are different types of baselines to consider:

- **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.
- **Iterative Baseline:** As updates or new data become available, an iterative baseline may be established, which builds upon the initial baseline with additional information.
- **Mid-lifecycle Baseline:** During the lifecycle of a product, significant changes or updates may necessitate the creation of a mid-lifecycle baseline, which serves as a new reference point for future submissions.

NEW SECTION 3.13 LINE EXTENSION

A new section, 3.13, has been added to the eCTD v3.1 specification, dedicated to line extensions. This addition provides specific guidance on how to submit and manage line extensions, which are increasingly relevant as pharmaceutical companies seek to expand the use of their approved products. The inclusion of this section highlights SAHPRA's commitment to providing clear instructions for various types of submissions.

UPDATE TO SECTION 4.3.4.20 ON MULTIPLE APPLICATIONS

Section 4.3.4.20 has been updated to reflect the differences in including clones, replicas, and duplicates in multiple applications. This update is crucial for sponsors who need to submit variations or related products, as it outlines the correct approach to handling these submissions within the eCTD framework.

INCLUSION OF 2.2.3 ROLLING REVIEW

The eCTD v3.1 now includes Section 2.2.3 on rolling reviews, recognizing the value of this approach in the development and submission of complex dossiers. Rolling reviews allow for the sequential submission of data as it becomes available, which can expedite the review process for new pharmaceuticals. This inclusion reflects SAHPRA's alignment with international best practices and its focus on efficiency in the regulatory review process.

REFERENCE TO THE SCHEMA UPDATED TO V3.1

The eCTD v3.1 specification references an updated schema, which defines the structure and format of the electronic submissions. This update is essential for ensuring that all submissions are compliant with the latest standards and requirements set by SAHPRA. The schema update is a critical component of the eCTD v3.1, providing a clear framework for the organization and presentation of regulatory information.

BUSINESS PROTOCOL AND PORTAL

SAHPRA's eCTD v3.1 implementation is supported by a business protocol that outlines the procedures and rules for electronic submissions. This protocol, along with the SAHPRA portal, provides a clear framework for sponsors to follow when submitting the eCTD sequences. The portal serves as the gateway for electronic submission, offering a user-friendly interface for document uploads and communication with SAHPRA.

ZA ECTD V3.1 SPECIFICATIONS AND REGIONAL CONSIDERATIONS

The ZA eCTD v3.1 specifications are tailored to the South African regulatory environment, considering regional considerations and requirements. These specifications ensure that submissions are relevant and appropriate for the local context, while also aligning with international standards to facilitate global harmonization of regulatory submissions.

MULTIPLE APPLICATION NUMBERS

One of the significant features of SAHPRA's eCTD v3.1 is the ability to handle multiple application numbers within a single submission. This is particularly useful for manufacturers that need to reference various applications or submit multiple products simultaneously. The system allows for clear identification and tracking of each application number, ensuring that the review process is organized and efficient.

VALIDATION CRITERIA V3.1

The South African Health Products Regulatory Authority (SAHPRA) has amended validation criteria with the release of its eCTD v3.1 specification. These criteria are designed to ensure that all regulatory submissions are accurate, consistent, and presented in a format that is easily accessible to reviewers.

Conclusion

SAHPRA's eCTD v3.1 specification introduces a range of updates and enhancements that are set to improve the regulatory submission process in South Africa. From the correction of typographical errors to the addition of new sections and definitions, these changes reflect SAHPRA's ongoing efforts to align with international standards and to facilitate a more efficient and effective review process. As the pharmaceutical industry continues to evolve, staying informed about updates like the eCTD v3.1 is essential for companies looking to maintain compliance and achieve successful outcomes in their regulatory submissions. And it also represents a significant milestone in the evolution of healthcare regulation in South Africa. By streamlining processes, enhancing surveillance, strengthening quality control, and embracing digital technologies, SAHPRA is not only keeping pace with global standards but is also setting a benchmark for regulatory excellence in the region. With a focus on safety, efficacy, and quality, SAHPRA's latest framework is poised to deliver tangible benefits to all stakeholders, ensuring that the health and well-being of the South African population remain a top priority.

Timeline:

- Implementation of eCTD v3.1 is voluntary beginning October 1st, 2024, and required beginning November 2024.
- SAHPRA invites applicants to engage in HPA application testing in a test environment with 5 applications for new submissions, 5 applications for variations, and 5 applications for renewals in December 2024, followed by application assessment and feedback.
- Based on testing input, the standards will be amended and refined in January/February 2025, but the Schema will remain unchanged.
- In March 2025, SAHPRA will begin the process of migrating legacy applications from the business processing system and freezing administration.
- The administration freezing period will be from March 24th to March 28th. If any applicant expects to submit applications to SAHPRA, they should contact SAHPRA on or before March 21st.
- SAHPRA will begin accepting new HPA applications, variations, and renewals from April 2025.

References: https://ectd.sahpra.org.za/

About Ennov

Ennov offers a unified compliance platform to power solutions that span all regulated business areas (Regulatory, Quality, PV, Clinical, Commercial). From leading pharmaceutical companies to start-up biotechs, we proudly serve over 300 companies and 300,000 users worldwide.

For more than 20 years, we have been developing innovative, powerful and easy-to-use software for regulated content, data and process management. Our solutions are designed and built to support the entire Life Sciences R&D continuum. Ennov is ISO 9001:2015 certified for all software products and processes and we boast a 100% success rate in customer audits.

Raleigh

223 S West St., Ste 1000
Raleigh, NC 27603, USA

+1 (833) 366-6887

Paris

149 avenue de France
75013 Paris, France

+33 (0)1 40 38 81 38

Cambridge

5 Eaton Court Road,
Colmworth Business Park
Eaton Socon, St Neots
Cambridgeshire PE19 8ER, UK

+ 44 1 480 21 22 23

Japan

CCI France Japon Nihonbashi
Honcho YS Building, 2F
2-2-2 Nihonbashi Honcho,
Chuo-ku
Tokyo 103-0023, Japan

+81-3-4500-6670