SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDANCE FOR THE SUBMISSION OF REGULATORY INFORMATION IN eSUBMISSION FORMAT

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration, as well as variations, of medicines in eSubmission 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. This format will only be accepted for a limited period.

Guidelines and application forms are available from the office of the Authority and the website.

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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient (also known as Drug Substance)
CD	Compact Disc
CD-ROM	Compact Disc Read-Only Memory
CTD	Common Technical Document
DTD	Document Type Definition
DVD	Digital Video Disc
eCTD	electronic Common Technical Document
eSubmission	electronic Submission
EMA	European Medicines Agency
ICH	International Council on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INN	International Non-proprietary Name
IPI	Inactive Pharmaceutical Ingredient
ISO	International Standards Organisation
IT	Information Technology
LCM	Life cycle management
ME&R	Medicines Evaluations and Registration
OCR	Optical Character Recognition
PDF	Portable Document Format
PHCR	Proposed Holder of Certificate of Registration
PI	Professional Information
PIL	Patient Information Leaflet
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
RAR	RoshalARchive
ToC	Table of Contents
Util	Utility folder in the eCTD Sequence. Contains technical files
XML	Extensible Markup Language
ZA/SA	South Africa

DEFINITIONS

Applicant	Organisation creating and submitting the eSubmission. Can either refer to the PHCR or HCR
Application number:	The application number is the official reference number assigned to the medicine application by SAHPRA. It remains with the dossier for its full life cycle and also in archiving.
Application identifier:	An eSubmission identifier is the application number used as the directory name in the top-level directory.
Dossier:	A collection of documents compiled by an applicant in compliance with South African legislation and guidelines to seek registration of a medicine, or any variations thereof. An application may comprise of several submissions.
eSubmission application:	A collection of electronic documents compiled by an applicant in compliance with South African legislation and guidelines to seek registration of a medicine, or any variations thereof.
eSubmission:	An eSubmission is an electronic submission in the format prescribed in this guideline that is supported by paper documents (e.g. some documents from Module 1, see appendix 2)
RAR:	A file format that supports data compression
Regulatory activity	A regulatory activity is a logical entity of submission activity (for example a new indication) with a defined start and end point (e.g. initial submission to final approval). It can also be defined as a collection of sequences covering the start to the end of a specific business process, e.g. an initial application for registration or a type II variation. It is a concept used to group together several business related sequences.
Submission / Sequence:	A single set of information and/or documents supplied by the applicant as a partial or complete application.
Validation:	Technical validation: Automatic validation will be performed on the eSubmission when loaded to ensure the structure conforms to SAHPRA criteria. Please refer to the eSubmission validation criteria document for more information. Content validation: The content validation is the evaluation of the contents of the submission by SAHPRA evaluators. Content validation can only occur after the submission has successfully been imported into the eSubmission review system. As a result of the content validation the Authority may ask for an updated sequence 0001 (or appropriate higher sequence).

1 PURPOSE AND SCOPE

This guideline is intended to assist pharmaceutical companies with the submission of regulatory information in an eSubmission format.

eCTD is the preferred format for submission to the South African Health Products Regulatory Authority (SAHPRA). eSubmissions will be accepted by the authority for a limited period of time. Please refer to the Roadmap (2.26) for more detail on the implementation timelines.

This document applies to all human medicines (pharmaceutical and biological). It does not apply to veterinary medicinal products or complementary medicines.

2 STRUCTURE OF SUBMISSIONS

2.1 Structure

Regulatory information must be structured in accordance with the Common Technical Document (CTD).

For eSubmission applications, the same folder and naming structure used for eCTD applies. The breakdown of the electronic submission should be in conformity with the ICH eCTD file naming and granularity for modules 2 to 5 (V3.2.2). The granularity of module 3.2.R used for eCTD submissions should be used in eSubmissions.

eSubmissions differ from eCTD submissions in that the XML files, util folder, checksum and style sheet are not present. Navigation through an eSubmission is based on the Tables of Contents and manual navigation through the folder structure.

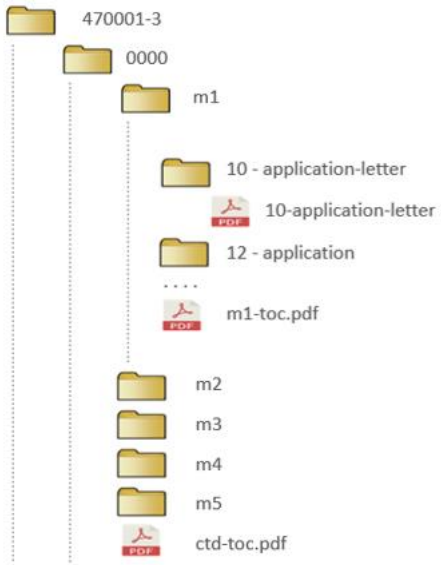

Figure 1: eSubmission folder structure (partially expanded)

2.2 Application identifier

The application number is to be used for the top-level directory (root directory). This will be the unique identifier for the application. In the case of multiple applications[1] the application number of the master application should be used as the eSubmission identifier. In the case of a clone application the application number of the originally registered product should be used as the eSubmission identifier. Please refer to the multiple submission guideline for further information.

The applicant has to email a request on the official company letterhead (PDF format) to applicationnumbers@sahpra.org.za with details of the application(s) to be submitted using the working code "eSubmission AGC". If a clone is applied for, the original application upon which the clone is based, should be clearly indicated. The request has to be submitted at least twelve weeks before the intended date of submission, to allow for four weeks for processing at the Authority. The proposed proprietary name and the type of data to be submitted in support of safety and efficacy should be indicated in the request.

The application number(s) will then be issued and will be valid for a period of eight weeks. If the application is not submitted within eight weeks, the applicant should submit a reason for the delay and request for an extension of the validity. Alternatively, the number may be cancelled and the applicant may have to apply for a new number.

Details of the name used for the root directory should always be included in the letter of application. The new application and subsequent submissions must use the same top-level directory name, e.g.

/470001-3/0000

/470001-3/0001

2.3 Submission sequence numbering

Sequence numbers, as they are defined for eSubmissions, are applicable for eSubmissions to ensure product history management of the application.

All files and folders in a submission in eSubmission format are to be placed under the sequence number folder.

The sequence number folder should be named using a four-digit number. The sequence number for the first submission should be 0000. Applicants are to provide an incremental number, unique within the same application for each new sequence they provide.

If a submission fails technical validation due to a technical error, the sequence number does not change when the application is submitted again. If the submission passes technical validation, but has content deficiencies, resolving these deficiencies requires an increment to the sequence number.

Note: The entire eSubmission needs to be re-submitted each time the applicant makes changes.

2.4 Variations

A baseline submission is preferred but not mandatory before a variation application can be submitted. The baseline can be submitted with the variation.

When submitting an application for variation, only submit the modules that are affected by the variation.

This variation application requires an increment to the sequence number.

[1] 2.40 Multiple submissions of the same application for registration with different proprietary names

2.5 Table of contents (ToCs) and bookmarks

ToCs always need to be provided by the applicant and should always be submitted in PDF format.

While it is preferred that documents in the eSubmission dossier are referenced from a hyperlinked ToC, this is not a mandatory requirement. If hyperlinks are used in the ToC, blue underlined text should be used to illustrate the hyperlinks to the individual documents.

In the case of small dossiers (e.g. for certain variations), especially where only one module besides Module 1 is concerned, it should be acceptable to only include a main ToC referring directly to the content documents. However, for larger submissions, the main ToC should refer to module ToCs.

The file containing the main ToC for the CTD should be named ctd-toc.pdf and be located in the four digit number named folder for the eSubmission. This folder comes next to the root or top level folder (see also section 2.1)

The files containing the module ToC should be named m1-toc.pdf, m2-toc.pdf, m3-toc.pdf, m4-toc.pdf and m5-toc.pdf and be located in the corresponding top level module folder.

An additional function may be provided to allow for easy navigation back to the ToC. This can be achieved by using a bookmark linked back to the previous level. This additional function is not mandatory, but when provided it will facilitate the assessment.

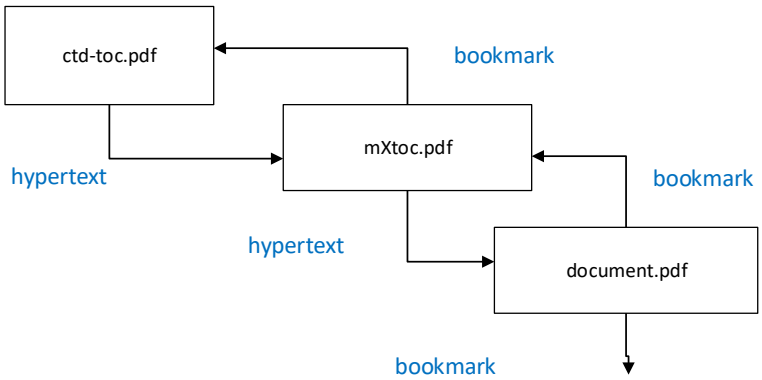

Figure 2: Principle for hypertext links and bookmarks if used in TOC

2.6 Submission formats

The eSubmission is intended as an electronic only submission. However, for operational and legal purposes distinct documents of Module 1 such as listed in Appendix 2 have to be submitted also as signed original paper versions.

The paper version is to be arranged in the same order as the electronic version. An electronic copy declaration should be submitted in Module 1.2.2.4 to confirm that the paper versions are identical to the PDF versions included in the eSubmission. As it is a declaration, it must be signed and dated and indicate the relevant sequence.

The current SAHPRA practices have to be taken into account to define which documents are needed for the submission types, and the documents detailed in Appendix 2 should be provided where applicable.

Please refer to other SAHPRA guidelines relating to applications for registration.

2.7 Moving from eSubmission to eCTD

Applicants may (and are encouraged to) switch from eSubmission to eCTD at the start of any new regulatory activity. Applicants however cannot change from eCTD back to eSubmission.

3 TECHNICAL REQUIREMENTS FOR SUBMISSIONS

3.1 Submission media

The following media formats will be accepted for eSubmissions (note SAHPRA does not return the submission media):

- CD-ROMs (conforming to ISO 9660 or ISO 13346)
- DVD-ROMS
- USB drives (2.0 or higher)

The electronic information or eSubmission should be directly readable and usable on SAHPRA's hardware (e.g. CD/DVD drive) using its own software. It is the policy of SAHPRA to maintain desktop configurations and IT infrastructure in line with common office standards.

The use of re-writable disks is not encouraged. When using re-writable disks, all open sessions must be closed before sending the CDs/DVDs.

In the case of a large application, provision of a single DVD over multiple CDs is required by SAHPRA, as this allows the technical validation and loading into the repository directly from the hard media, without the need to first recompile the eSubmission on a server. Applicants should only use USB drives if the application cannot fit onto a single DVD.

The submission media should be packed adequately to prevent damage to the media. All the contained media units should be appropriately labelled as described below. If a USB drive is used, it should be packaged in a sealed envelope.

Each CD, DVD or USB submitted with an eSubmission should include the following label information, clearly presented and printed on the media, or attached securely to the USB drive (for example using a tag that is securely attached to the USB body)

- The applicant's name
- The proprietary name(s)
- The registration number or application number
- The International Non-proprietary Name(s) (INN) of the product
- The sequence number of the eSubmission contained on the CD/DVD/USB
- The submission date (MM-YYYY)

3.2 Compression and password protection/security settings

The applicant is required not to apply any compression to the submission or the files inside the submission. Therefore, the data on the media should not be packed into a zip-file, rar-file or any other file format that has been compressed.

One-time security settings or password protection of electronic submissions for security purposes is not acceptable during transportation from the applicant to SAHPRA. Applicants should also not include any file level security settings or password protection for individual files in the eSubmission. The file settings should allow for printing, annotations to the documents, and selection of text and graphics. Internal security and access control processes in the regulatory authority will maintain the integrity of the submitted files.

Encryption is not considered necessary if the information is sent using a physical media. The applicant should assume all responsibility for the media until it is delivered to SAHPRA.

The following points should be noted in relation to security:

- The physical security of the submission during transportation/transmission is the responsibility of the applicant.
- Once received by SAHPRA, security and submission integrity is the responsibility of the authority.

3.3 PDF files

Portable Document Format (PDF) is an electronic format that is open, de facto, and published and created by Adobe Systems Incorporated (http://www.adobe.com). No specific products from Adobe or any other company are necessary to produce PDF documents.

The following points can be made in relation to PDF files:

- Files should be PDF v1.4, 1.5, 1.6 or 1.7 and should be legible with the Acrobat Reader search plug in or any other freeware viewer; PDF files should be saved as ”Optimised” to reduce the size and allow faster opening when viewed via an internet connection. The use of additional software to navigate and work with the files is not acceptable.
- PDF files produced from an electronic source document are preferred to PDF files generated from scanned paper since such 'electronic' PDF files provide the maximum functionality to the reviewers in terms of search capabilities and copy & paste functionality.
- Expert Reports and the Overviews/Summaries in the CTD Module 2 should preferably be generated from an electronic source document.
- If scanning is unavoidable, legibility and file size should be balanced; the following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid gray-scale or colour where possible, use only lossless compression techniques. The file must be searchable (OCR scanned).
- The maximum individual acceptable file size is approximately 200 MB. If a file size exceeds 200 MB, the file should be split into two files. The file size should ensure clarity, speed of download and ease of review.
- Fonts should be chosen of a type, colour and size such that they allow for easy reading of documents on screen (1024 x 768 pixels) or after printing.
- All fonts used in a document (except Times New Roman, Arial and Courier) should be embedded, including all the characters for the font. The number of fonts used in a document should be limited and customised fonts be avoided. If colours other than black are used, colour reproduction after printing should be tested before submission; the print area for pages should fit on an A4 sheet of paper; margins should allow binding without affecting readability.

3.4 File naming conventions

The eCTD file naming conventions described in the ICH M2 eCTD Specification and the South African Specification for eCTD Module 1 are to be used.

If an applicant wishes to submit multiple files in one section, where only one highly recommended name is available, this can be achieved using a variable suffix to the filename (e.g. pharmaceutical-development-container.pdf).

3.5 Additional files in Word format

SAHPRA requires Word documents for the following documents, in addition to the PDF for the purposes of review and document manipulation:

- Module 1.2.1 Application form
- Module 1.3:
  - Professional Information
  - Patient Information Leaflet
  - Label
- Module 3.2.R.8: SCoRE document

SAHPRA requires only Word documents for the following documents:

- BTIF (Bioequivalence Trial Information Form)
- Biowaiver template
- ME&R reliance template

Word files should be placed on the same data carrier, alongside the 0000 (or appropriate) eSubmission sequence, not within it (see Figure 3). The folder should be called “eSubmission sequence-workingdocuments” (e.g. 0000-workingdocuments)” with a substructure as follows:

- 0000-Application form
- 0000-Product information

Within this folder, for the following files in Word format, the following naming convention applies:

- For the Application Form
  af_productname_submissiontype_date.doc
- For the professional information:
  pi_productname_submissiontype_date.doc
- For the patient information leaflet:
  pil_productname_submissiontype_date.doc
- For the label:
  label_productname_submissiontype_date.doc
- For the SCoRE:
  score_productname_submissiontype_date.doc
- For the BTIF:
  btif_productname_submissiontype_date.doc
- For the biowaiver template:
  biowaiver_productname_submissiontype_date.doc
- For the ME&R reliance template:
  reliancetemplate_productname_submissiontype_date.doc

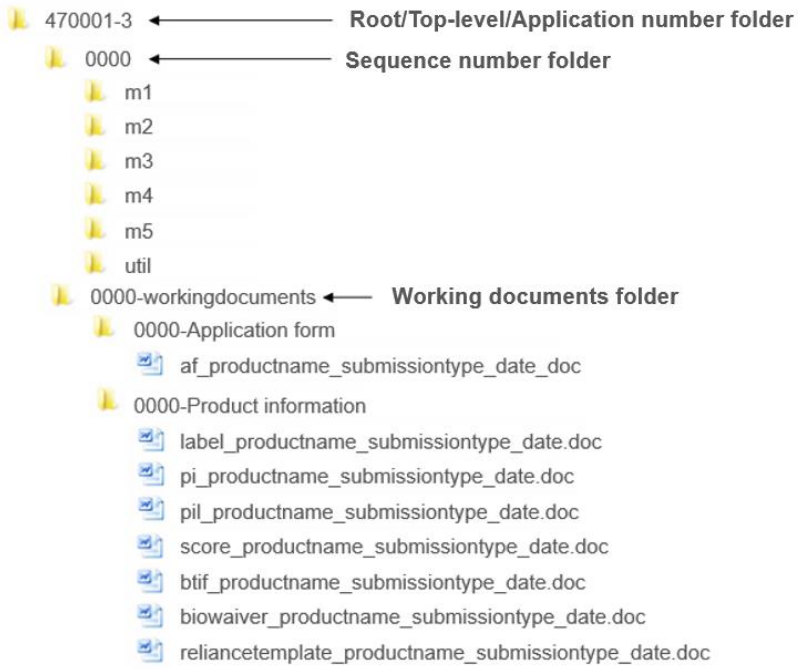

Figure 3: Location of working documents

3.6 Inclusion of correspondence documentation

The term ”correspondence” applies to all communications (documents) that are exchanged between an applicant and the authority in the context of a regulatory activity but which do not have a formal designated placeholder within the eSubmission structure.

Only the minimum correspondence that relates directly to the content of the dossier should be included in submissions to SAHPRA, e.g. committee recommendations should be included as an annex to the letter of application in Section 1.0 when submitting a response. All other correspondence should be exchanged outside the eSubmissions via the usual means.

3.7 Letter of application

An administrative letter of application in both paper and Portable Document Format (PDF) should accompany submissions in eSubmission format. The PDF should be a scan of the originally signed document and must be searchable (OCR scanned).

This letter should always state the context of the submission, e.g. the submission type and the application or registration number.

The paper and PDF letters must have the same content.

The letter of application in the submission in eSubmission format is located in the folder 1.0 of the ZA Module 1.

In case of a technical rejection, the replacement sequence needs to include the original letter of application of the rejected sequence in Module 1.0 in addition to the new letter of application for the

replacement sequence. The file names of both letters should be clear. For example, a follow-up sequence due to the first query screening response would contain 2 letters, the original letter as well as the response letter. The letter should at least contain the following information:

- Date
- The applicant's name and address
- The proprietary name(s)
- Registration number or Application number
- Dosage form
- Dosage strength(s)
- The International Non-proprietary Name(s) (INN) of the product
- The submission type
- A description of the submission
- Number of CDs/DVDs/USBs provided
- Contact details in case of technical validation issues (e.g. e-email address that can receive e-mails with attachment, and contact number)
- The working code according to the General Information guideline. The working code should be preceded by eSubmission, e.g. "eSubmission ANA".

The following statement must be included:

- For CDs/DVDs: "We confirm that the CD/DVD-burning session is closed and the submission is checked with an up-to-date and state-of-the art virus checker: [name of the antivirus software and version of the virus checker] and is virus-free".
- For USBs: "The submission is checked with an up-to-date and state-of-the art virus checker: [name of the antivirus software and version of the virus checker] and is virus-free".

In addition, when submitting an application via eSubmission, a brief description must be included stating the reasons why eSubmission was used instead of the SAHPRA preferred eCTD format.

The tracking of the submitted sequences in a tabular format should be included as an annex to the letter, as per the following example:

Date of submission	Sequence number	Submission type	Related eSubmission sequence	Regulatory activity/ Submission description	Regulatory status (submitted / approved / rejected

The letter (paper version) must be signed.

All annexes to the letter should be included with the letter, and be bookmarked.

3.8 Virus check

The applicant is responsible for checking the submission for viruses and for informing SAHPRA of the type of software used for this purpose.

Checking should be performed with at least one, but preferably more, up-to-date virus checkers and a statement must be included in the letter of application (see section 3.7)

After receipt at SAHPRA an internal virus check will be performed. Detection of a virus will results in the refusal of the eSubmission.

4 TECHNICAL VALIDATION

4.1 Validation rules

The technical validation of an eSubmission is a separate activity to the content validation of a submission and takes place irrespective of the type of the submission. SAHPRA has adopted a common set of technical validation criteria against which all eSubmissions can be checked using eSubmission review and validation. The validation criteria are derived from the guidelines contained in this document.

Two categories of validation rules apply “Pass/Fail” and “Best Practice”.

Pass/Fail Criteria - These are validation criteria that can either be passed or failed. An eSubmission that fails to meet one or more of these criteria will be reported back to the applicant for fixing and resubmission (using the same four digit folder name if applicable).

Best Practice Criteria - The applicant should make every effort to address these areas before the eSubmission is submitted to the Authority. An eSubmission that fails to meet one or more of these criteria may still be accepted by the Authority during technical validation

Note: Errors found during the content validation should be resolved through the re-submission of the complete application. If using a sequential numbering system, this submission containing the required documents should have the next number.

4.2 Validation process

Applicants must use the eSubmission validation template to ensure that the submission complies with business validation rules before submission.

SAHPRA will carry out the following process on receipt of an eSubmission:

(1) Administrative compliance check *(see section A.1 of the Validation Template)*

(2) Technical validation: This will be performed in a single step *(see section A.2 of the Validation Template)*

(3) Business validation: Content check *(see section A.3 of the Validation Template)*

(4) Technical screening (*see sections B, C, D, E of the Validation Template*)

In case of technical validation issues, the application will be returned to the applicant with a report identifying issues to be corrected. The corrected sequence has to be submitted with the same sequence number.

If no technical validation issues are identified the eSubmission will be imported into the review system for business validation and technical screening. The applicant will be notified of successful validation for the first sequence submitted (i.e. 0000). For follow-up sequences the applicant will only be notified if there are technical or business validation issues.

5 BASELINE SUBMISSIONS

A baseline eSubmission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to SAHPRA but in paper.

A baseline may assist SAHPRA in referencing historical information, and while it is preferred that candidates submit a baseline if eSubmission is used, it is not mandatory. Baseline submissions should not be submitted during an ongoing regulatory activity. The baseline should always be a separate submission and should never include new applications.

The baseline submission should reflect the status of the most recently approved dossier. The sections provided to make up a baseline can be defined by the applicant, but any omissions should not render the submitted content misleading. A signed declaration must also be submitted in Section 1.2.2.4 stating that the content/data of the submitted modules in eSubmission format is identical to the current approved documents and that there have been no changes to the dossier content as a result of the provision of an eSubmission. It is not acceptable to exclude any information from the original dossier unless it has been updated by a regulatory process (e.g. variation). It is not necessary to include a SCoRE document in a baseline.

The baseline should preferably consist of high quality electronic source document, but good quality scanned images would also be acceptable in these cases, preferably with OCR to facilitate text searching.

In the majority of cases, an eSubmission baseline submission will be provided as sequence 0000 for a product where there has been no previous eSubmission. However, for a product with an ongoing lifecycle SAHPRA would also accept a baseline submission within the lifecycle.

Only a technical and business validation will be carried out on the eSubmission sequence. There is no content validation and no evaluation process involved in eSubmission baseline submissions which is a mere conversion of what has already been submitted

A baseline always has to be submitted as a separate sequence. It is possible to submit a baseline sequence as a separate sequence together with a variation.

The following has to be considered:

Timing of the baseline submission in eSubmission format:

- Preferred option: At the beginning of the transition from paper to eSubmission as sequence 0000
- For products with variations planned for Module 3
- Before or with a variation (of e.g. Module 3) BUT as a separate sequence (e.g. baseline is 0000 and variation applied for is 0001)
- Before or with an application for a clone BUT as a separate sequence

When submitting changes to Module 3, it will be expected that in most cases the full section Drug Substance and/or Drug Product will be submitted. Exceptions (when such submissions will not be of added value) should be justified in the letter of application.

In principle, all CTD subheadings should be addressed. Statements justifying absence of data for specific CTD sections should be provided in the relevant Quality Overall Summary when relevant. If a QOS does not exist in the current approved dossier, then the justification for absence of data can be included in the cover letter. To reflect the status most recently approved, all the documents of Module 1 relevant to the registration need to be included into the baseline submission.

6 SUBMISSION

The paper copies and the hard media should be submitted jointly.

The eSubmission on DVD/CD/USB should be submitted to SAHPRA at the following address:

The Chief Executive Officer
South African Health Products Regulatory Authority
Building 38a
CSIR
Meiring Naudé Road
Brummeria
Pretoria
South Africa

7 UPDATE HISTORY

Date	Reason for update	Version & publication
July 2019	First publication for implementation	v1 July 2019

8 APPENDICES

Appendix 1: eSubmission Reference Documents

2.26 Implementation Roadmap

6.30 New registration validation template for applications in eSubmission format

Appendix 2: List of documents requested additionally in paper format

One copy of each document is required.

Module No	Name of document
1.0	Letter of Application
1.2.1	Application form
1.2.2.1	Proof of payment with copy of letter of application in a separate envelope (when relevant)
1.2.2.4	Electronic copy declaration
1.5.2.2.2	Original or certified copy of registration certificate (when relevant)
1.5.2.3	Affidavit by Responsible Pharmacist
1.7.9.1	Letters of cession and acceptance (when relevant)
1.8	Validation template (up to the end of section A.3.)