

MEDICINES CONTROL COUNCIL



SOUTH AFRICAN eCTD VALIDATION CRITERIA

This document is intended to provide requirements to applicants wishing to submit applications for the registration 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 the office of the Registrar of Medicines and the website.

First publication released for pilot implementation and comment

March 2013

REGISTRAR OF MEDICINES
MS M HELA

| ZA No. | CATEGORY | VALIDATION CRITERION | SEVERITY |
|--------|----------------|--|----------|
| 1 | Checksum | The checksum-type attribute must have the value md5 or MD5. | P/F |
| 2 | Checksum | The checksum of the index.xml, when calculated by the validation tool, should match the check-sum provided in the index-md5.txt | P/F |
| 3 | DTD | The index.xml/za-regional.xml are well-formed and valid when compared to the DTD versions provided in the 'util/dtd' folder | P/F |
| 4 | DTD | The checksum of the ICH and ZA-M1 DTDs and .mod files found in the util/dtd folder is the same as that of the corresponding DTDs and .mod files located in the eCTD validator's installation folder (subfolder DTDs), or the same as the published reference DTDs if available. Please refer to document 2.27 eCTD Checksums for the checksum of the ZA DTD. | P/F |
| 5 | DTD (ZA) | A valid ZA M1 DTD exists | P/F |
| 6 | DTD (ICH) | A valid ICH DTD exists | P/F |
| 7 | File Reference | There are no unreferenced files in the root folder, M1, M2, M3, M4 & M5 folders (including sub-folders but excluding 'util' subfolders, the index-md5.txt and index.xml) | P/F |
| 8 | Files/folders | All file formats used are valid (MS Word files, if requested, should not be included in the eCTD backbone but provided separately - see Chapter 4.7 in the Guidance for Submission of Regulatory Information in eCTD Format) | P/F |
| 9 | Files/folders | Total folder/file path does not exceed 180 characters | P/F |
| 10 | Files/folders | File names do not exceed 64 characters | P/F |
| 11 | Files/folders | All characters used in referenced file names are valid (according to the name requirements of the ICH eCTD Specification) | P/F |
| 12 | index.xml | The index.xml/za-regional.xml is present and is placed in a correct position (i.e. ensure there is an ZA Module 1 backbone file named za-regional.xml in the folder xxxx/m1/za) | P/F |
| 13 | Modified File | The syntax of the modified file entry is in accordance with ICH 3.0 or 3.2: If the value of the operation attribute is new, the eCTD Validator verifies that: the modified file must not exist / the title is given / href must exist. | P/F |
| 14 | Modified File | The syntax of the modified file entry is in accordance with ICH 3.0 or 3.2: If the value of the operation attribute is append, the eCTD Validator verifies that: the modified file must exist / the title is given / href must exist. | P/F |
| 15 | Modified File | The syntax of the modified file entry is in accordance with ICH 3.0 or 3.2: If the value of the operation attribute is replace, the eCTD Validator verifies that: the modified file must exist / the title is given / href must exist. | P/F |

| ZA No. | CATEGORY | VALIDATION CRITERION | SEVERITY |
|--------|------------------|---|----------|
| 16 | Modified File | The syntax of the modified file entry is in accordance with ICH 3.0 or 3.2: If the value of the operation attribute is delete, the eCTD Validator verifies that: the modified file must exist / the title is required / href must not exist. | P/F |
| 17 | Modified File | The syntax of the modified file entry is in accordance with ICH 3.0 or 3.2: If the operation is append, replace or delete, then the modified file attribute must use the correct syntax (i.e. modified-file=" ../0001/index.xml#a1234567") | P/F |
| 18 | Security | There is no security setting or password protection on any individual file | P/F |
| 19 | Sequence Number | The sequence number is 4 digits (i.e. numbers between 0000 and 9999) | P/F |
| 20 | Sequence Number | The sequence number has not already been used* | P/F |
| 21 | Sequence Number | The sequence folder name matches the sequence number in the za-envelope in za-regional.xml | P/F |
| 22 | Util Folder | A 'util' folder exists and is in the correct location (xxxx/util) | P/F |
| 23 | xlink:href | xlink:href conforms to the eCTD standard (using the relative path to the file and file name) | P/F |
| 24 | xlink:href | If the operation is new, append or replace, then xlink:href should point to a document | P/F |
| 25 | xlink:href | If the operation is delete, then xlink:href should be blank | P/F |
| 26 | XML | XML:Every leaf or node extension 'title' attribute is not empty | P/F |
| 27 | xlink:href | No references in index files (xlink:href) should target files outside the eCTD life cycle | P/F |
| 28 | Files/folders | Individual files do not exceed 100 MB in size | BP |
| 29 | ID Attribute | The ID attribute value starts with a letter or underscore character | BP |
| 30 | Leaf | Checks for elements not having any leaf child nodes - all the lowest level heading elements included in the submission contain at least one leaf | BP |
| 31 | PDF | PDF Format is PDF 1.4, 1.5 , 1.6, or 1.7 | BP |
| 32 | PDF | There are no broken links in a PDF document | BP |
| 33 | PDF | PDFs have the 'Fast Web Access' option active | BP |
| 34 | PDF | All PDF links and Hyperlinks are relative (are not absolute or rooted) | BP |
| 35 | Modified File | No modified file references an invalid document: If the operation is append, replace or delete, then the modified file attribute should point to a valid document (although if submissions are received non-sequentially then it is possible that a sequence refers to a file in a later sequence not yet received by the agency, so warning only should be given)* | BP |
| 36 | PDF initial view | Bookmarks pane should be visible if bookmarks are included with a PDF document | BP |

| ZA No. | CATEGORY | VALIDATION CRITERION | SEVERITY |
|--|-----------------|---|-----------------|
| 37 | Checksum | The regenerated checksum for every referenced file is the same as each associated checksum provided in the backbone file (e.g. za-regional.xml) | BP |
| 38 | PDF | PDFs open in "most recent view" (i.e. 'inherit zoom' for bookmarks and links, and 'default' in open dialogue box. (ICH eCTD spec p7-4)). | BP |
| 39 | PDF | All files should have one and only one file extension. The file extension should be used to indicate the format of the file. | BP |
| * This criterion can only be validated in the lifecycle (not part of a stand-alone validation) | | | |
| Description of Severity | | | |
| P/F | Pass / Fail | These are validation criteria that can either be passed or failed. eCTDs that fail to meet one or more of these criteria will be returned to the applicant for fixing and resubmission with the same sequence number. | |
| BP | Best Practice | <p>Any deviation from the criterion should always be reported by the validation tool. It is considered good practice to ensure that these validation criteria are correct in the submitted eCTD. The applicant should make every effort to address these areas before the eCTD is submitted.</p> <p>eCTDs that fail to meet one or more of these criteria will be still be accepted during technical validation.</p> <p>These criteria assess factors that affect the overall ease of use of the eCTD. All tool vendors should include these criteria in their validation tools to enable applicants to produce eCTDs that are easier to use.</p> | |

LEGEND

Black

These entries are fixed text for folder and file names according to the ZA and ICH specifications. The level of adherence to these names is specified in the eCTD validation criteria.

Red

These entries are variable text for folder and file names according to the ZA and ICH specifications. In all folder locations containing file names entirely in red text or files with **-var** components, multiple files are accepted.

Blue (compendial)

If the folder name starts with this text, then component filenames below are entirely variable. If the foldername does not start with this word, then the fixed filenames should be followed.

Bold, no file extension

These entries indicate folder names, and are coloured in accordance with the legend above

Regular, with file extension (.pdf)

These entries indicate file names, and are coloured in accordance with the legend above

Use of Additional Folders

multiple branches possible

At these locations, a complete branch of the table of contents can be added

optional folder

At these locations, one or more optional subfolders may be used, (also as nested folders, i.e. folders within folders) but files can also be placed directly at this location. The subfolders and single files can also be used beside each other at the same level.

folder required and

additional folders optional

At these locations, there must be a subfolder if content is provided. Optional additional subfolders are also allowed.

In all other locations, additional folders are not allowed.

product-name**0000**

index.xml

index-md5.txt

m1**za**

za-regional.xml

10-application-letterapplication-letter-**var**.pdf**12-application****121-application-form**application-form-**var**.pdf**122-annexes****1221-proof-of payment**proof-of-payment-**var**.pdf**1222-letter-of-authorisation**letter-of-authorisation-**var**.pdf**1223-dossier-product-batch-information**dossier-product-batch-information-**var**.pdf**1224-electronic-copy-declaration**electronic-copy-declaration-**var**.pdf**1225-cv-pharmacovigilance**cv-pharmacovigilance-**var**.pdf**1226-api-change-control**api-change-control-**var**.pdf**1227-vamf-certificate**vamf-certificate-**var**.pdf**1228-pmf-certificate**pmf-certificate-**var**.pdf**13-za-labelling-packaging****131-sapi****1311-pi**

- pi-var.pdf
- 1312-stdrefs**
 - stdrefs-var.pdf
- 132-pil**
 - pil-var.pdf
- 133-labels**
 - label-var.pdf
- 134-braille**
 - braille-var.pdf
- 14-expert-information**
 - 141-quality**
 - quality-var.pdf
 - 142-non-clinical**
 - non-clinical-var.pdf
 - 143-clinical**
 - clinical-var.pdf
- 15-specific-requirements**
 - 151-literature-based**
 - literature-based-var.pdf
 - 152-amendment**
 - 1521-amendment-schedule**
 - amendment-schedule-var.pdf
 - 1522-medicine-register**
 - medicine-register-var.pdf
 - 1523-affidavit**
 - affidavit-var.pdf
 - 153-proprietary-name**
 - proprietary-name-var.pdf
 - 154-gmo**
 - gmo-var.pdf
 - 155-pi-amendment**
 - pi-amendment-var.pdf
- 16-environ-risk-assessment**
 - 161-nongmo**
 - nongmo-var.pdf
 - 162-gmo**
 - gmo-var.pdf
- 17-gmp**
 - 171-last-inspection**
 - last-inspection-var.pdf
 - 172-inspection-report-or-equivalent**
 - inspection-report-var.pdf
 - 173-gmp-certificate**
 - gmp-certificate-var.pdf
 - 174-release**
 - 1741-api**
 - api-var.pdf
 - 1742-ipi**
 - ipi-var.pdf
 - 1743-fprc-tests**
 - fprc-tests-var.pdf
 - 1744-fprc-criteria**
 - fprc-criteria-var.pdf
 - 175-contract-confirmation**
 - contract-confirmation-var.pdf
 - 176-cpp**
 - cpp-var.pdf
 - 177-sapc-reg**
 - sapc-reg-var.pdf
 - 178-comp-reg**
 - comp-reg-var.pdf
 - 179-docs-phcr**
 - phcr-var.pdf
 - 1710-sample-documents**
 - 17101-sample-submission-confirmation**
 - confirmation-sample-var.pdf
 - 17102-sample-bmr**
 - sample-bmr-var.pdf
 - 17103-sample-coa**

- sample-coa-var.pdf
 - 1711-manufacturing-permit**
 - manufacturing-permit-var.pdf
 - 1712-inspection-flow-diagram**
 - inspection-flow-diagram-var.pdf
 - 1713-organogram**
 - organogram-var.pdf
 - 18-compliance-screening**
 - compliance-screening-var.pdf
 - 19-indiv-patient-data**
 - indiv-patient-data-var.pdf
 - 110-foreign-reg-status**
 - 1101-countries-same-appl**
 - countries-same-appl-var.pdf
 - 1102-foreign-reg-certif-or-ma**
 - foreign-reg-cert-or-ma-var.pdf
 - 1103-foreign-pi**
 - foreign-pi-var.pdf
 - 1104-data-set-similarities**
 - data-set-similarities-var.pdf
 - 111be-trial-info**
 - be-trial-info-var.pdf
 - 112-paediatric-dev-program**
 - paediatric-dev-program-var.pdf
 - 113-risk-management-plan**
 - risk-management-plan-var.pdf
- m2**
- 22-intro**
 - introduction-var.pdf
 - 23-qos**
 - qos-var.pdf
 - OR
 - introduction-var.pdf
 - drug-substance-var.pdf
 - drug-product-var.pdf
 - appendices-var.pdf
 - 24-nonclin-over**
 - nonclinical-overview-var.pdf
 - 25-clin-over**
 - clinical-overview-var.pdf
 - 26-nonclin-sum**
 - introduction-var.pdf
 - pharmacol-written-summary-var.pdf
 - pharmacol-tabulated-summary-var.pdf
 - pharmkin-written-summary-var.pdf
 - pharmkin-tabulated-summary-var.pdf
 - toxicology-written-summary-var.pdf
 - toxicology-tabulated-summary-var.pdf
 - 27-clin-sum**
 - summary-biopharm-var.pdf
 - summary-clin-pharm-var.pdf
 - summary-clin-efficacy-var.pdf
 - summary-clin-safety-var.pdf
 - literature-references-var.pdf
 - synopses-indiv-studies-var.pdf
- m3**
- 32-body-data**
 - 32s-drug-sub**
 - drug-substance** multiple branches possible
 - 32s1-gen-info**
 - nomenclature-var.pdf
 - structure-var.pdf
 - general-properties-var.pdf
 - 32s2-manuf**
 - manufacturer-var.pdf
 - manuf-process-and-controls-var.pdf
 - control-of-materials-var.pdf
 - control-critical-steps-var.pdf
 - process-validation-var.pdf

- manuf-process-development-**var**.pdf
- 32s3-charac**
 - elucidation-of-structure-**var**.pdf
 - impurities-**var**.pdf
- 32s4-contr-drug-sub**
 - 32s41-spec**
 - specification-**var**.pdf
 - 32s42-analyt-proc**
 - analytical-procedure**.pdf
 - 32s43-val-analyt-proc**
 - validation-analyt-procedure**.pdf
 - 32s44-batch-analys**
 - batch-analyses-**var**.pdf
 - 32s45-justif-spec**
 - justification-of-specification-**var**.pdf
- 32s5-ref-stand**
 - reference-standards-**var**.pdf
- 32s6-cont-closure-sys**
 - container-closure-system-**var**.pdf
- 32s7-stab**
 - stability-summary-**var**.pdf
 - postapproval-stability-**var**.pdf
 - stability-data-**var**.pdf
- 32p-drug-prod**
 - drug-product** **multiple branches possible**
 - 32p1-desc-comp**
 - description-and-composition-**var**.pdf
 - 32p2-pharm-dev**
 - pharmaceutical-development-**var**.pdf
 - 32p3-manuf**
 - manufacturers-**var**.pdf
 - batch-formula-**var**.pdf
 - manuf-process-and-controls-**var**.pdf
 - control-critical-steps-**var**.pdf
 - process-validation-**var**.pdf
 - 32p4-contr-excip**
 - excipient** **multiple branches possible**
 - specifications-**var**.pdf
 - analytical-procedures-**var**.pdf
 - validation-analyt-procedures-**var**.pdf
 - justification-of-specifications-**var**.pdf
 - compendial-excipients** **multiple branches possible**
 - specifications.pdf
 - analytical-procedures.pdf
 - validation-analyt-procedures.pdf
 - justification-of-specifications.pdf
 - excipients-human-animal-**var**.pdf
 - novel-excipients-**var**.pdf
 - 32p5-contr-drug-prod**
 - 32p51-spec**
 - specifications-**var**.pdf
 - 32p52-analyt-proc**
 - analytical-procedure**.pdf
 - 32p53-val-analyt-proc**
 - validation-analytical-procedures**.pdf
 - 32p54-batch-analys**
 - batch-analyses-**var**.pdf
 - 32p55-charac-imp**
 - characterisation-impurities-**var**.pdf
 - 32p56-justif-spec**
 - justification-of-specifications-**var**.pdf
 - 32p6-ref-stand**
 - reference-standards-**var**.pdf
 - 32p7-cont-closure-sys**
 - container-closure-system-**var**.pdf
 - 32p8-stab**
 - stability-summary-**var**.pdf
 - postapproval-stability-**var**.pdf
 - stability-data-**var**.pdf

| | | | |
|------------------------------|---|---|--|
| 32a-app | | | |
| 32a1-fac-equip | manufacturer facilities-and-equipment-report.pdf | optional folder | |
| 32a2-advent-agent | substance adventitious-agents-report.pdf | optional folder | |
| 32a3-excip-substance | substance substance.pdf | optional folder | multiple branches possible In line with ICH eCTD specification, "The directory/file structure would typically follow that of the drug substance section in Module 3.2.S." |
| 32r-reg-info | availability overview.pdf ref-prd-var.pdf coa-var.pdf avail-var.pdf | folder required and additional folders optional | |
| | parent-api-diff-sites statement.pdf | folder required and additional folders optional | |
| | cep cep-var.pdf | folder required and additional folders optional | |
| | multiple-api-mnf comp-rep-var.pdf comp-results-var.pdf compliance-guidelines-var.pdf coa-var.pdf | folder required and additional folders optional | |
| | med-dev med-dev-var.pdf | folder required and additional folders optional | |
| | animal-human-orig origin-var.pdf | folder required and additional folders optional | |
| | bmr bms-var.pdf | folder required and additional folders optional | |
| | other other-var.pdf | folder required and additional folders optional | |
| 33-lit-ref | reference.pdf | | |
| m4 | | | |
| 42-stud-rep | | | |
| 421-pharmacol | | | |
| 4211-prim-pd | study-report study-report.pdf | optional folder | |
| 4212-sec-pd | study-report study-report.pdf | optional folder | |
| 4213-safety-pharmacol | study-report study-report.pdf | optional folder | |
| 4214-pd-drug-interact | study-report study-report.pdf | optional folder | |
| 422-pk | | | |
| 4221-analyt-met-val | study-report study-report.pdf | optional folder | |
| 4222-absorp | study-report study-report.pdf | optional folder | |
| 4223-distrib | study-report study-report.pdf | optional folder | |
| 4224-metab | study-report study-report.pdf | optional folder | |
| 4225-excr | study-report study-report.pdf | optional folder | |

| | | |
|-------------------------|-----------------|--|
| 4226-pk-drug-interact | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4227-other-pk-stud | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 423-tox | | |
| 4231-single-dose-tox | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4232-repeat-dose-tox | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4233-genotox | | |
| 42331-in-vitro | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42332-in-vivo | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4234-carcigen | | |
| 42341-lt-stud | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42342-smt-stud | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42343-other-stud | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4235-repro-dev-tox | | |
| 42351-fert-embryo-dev | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42352-embryo-fetal-dev | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42353-pre-postnatal-dev | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42354-juv | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4236-loc-tol | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 4237-other-tox-stud | | |
| 42371-antigen | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42372-immunotox | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42373-mechan-stud | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42374-dep | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42375-metab | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42376-imp | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 42377-other | | |
| study-report | optional folder | |
| study-report.pdf | | |
| 43-lit-ref | | |

| | | |
|--|-------------------------|---|
| | reference.pdf | |
| m5 | | |
| 52-tab-list | tabular-listing-var.pdf | |
| 53-clin-stud-rep | | |
| 531-rep-biopharm-stud | | |
| 5311-ba-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5312-compar-ba-be-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5313-in-vitro-in-vivo-corr-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5314-bioanalyt-analyt-met | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 532-rep-stud-pk-human-biomat | | |
| 5321-plasma-prot-bind-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5322-rep-hep-metab-interact-stud | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5323-stud-other-human-biomat | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 533-rep-human-pk-stud | | |
| 5331-healthy-subj-pk-init-tol-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5332-patient-pk-init-tol-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5333-intrin-factor-pk-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5334-extrin-factor-pk-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5335-popul-pk-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 534-rep-human-pd-stud | | |
| 5341-healthy-subj-pd-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5342-patient-pd-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 535-rep-effic-safety-stud | indication | |
| 5351-stud-rep-contr | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5352-stud-rep-uncontr | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5353-rep-analys-data-more-one-stud | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 5354-other-stud-rep | study-report | folder required and additional folders optional |
| | study-report.pdf | |
| 536-postmark-exp | study-report.pdf | |
| 537-crf-ipl | study | optional folder |

- filename.pdf
- 54-lit-ref**
 - reference.pdf
- util**
 - dtd**
 - za-regional.dtd
 - za-envelope.mod
 - za-leaf.mod
 - ich-ectd-3-2.dtd
 - style**
 - ectd-2-0.xsl
 - za-regional.xsl

UPDATE HISTORY

| Date | Reason for update | Version & publication |
|-------------|--|----------------------------------|
| Feb 2013 | First publication as working document | v1_7 working document Feb 2013 |
| March 2013 | Publication for pilot implementation and comment | v1 March 2013 |