MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

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Questions & Answers
Implementation of eCTD in South Africa

This document is intended to provide clarity on guidelines and specifications for 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.

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DR JC GOUWS
REGISTRAR OF MEDICINES

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ABBREVIATIONS and ACRONYMS

Act	The Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended
API	Active Pharmaceutical Ingredient
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
EU	European Union
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
MCC	Medicines Control Council
Q&A	Question and Answer documents
Swissmedic	Swiss Agency for Therapeutic Products
ZA/SA	South Africa

DEFINITIONS

Refer to the **Guidance for the Submission of Regulatory Information in eCTD Format**

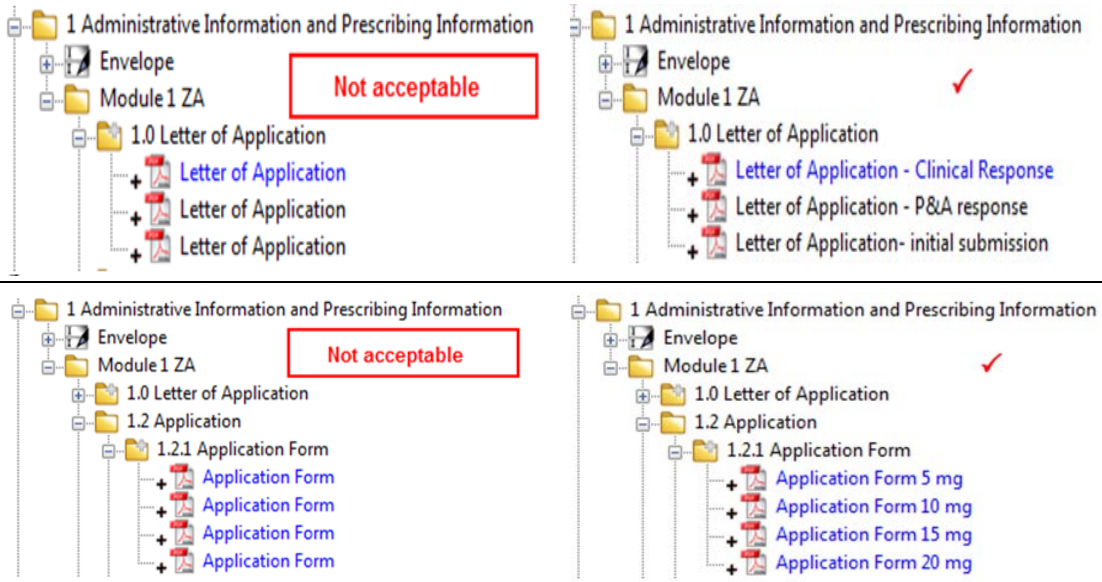
1 Introduction

This document is intended to explain requirements included in the guidelines and specifications for use and submission of applications for registration of medicines in eCTD format.

2 Questions about the Technical Requirements

2.1	Related sequences – must it be left open, or must <none> be included similar to Swiss?
	When a new Regulatory activity is started and there is no related sequence, the related sequence should be indicated as <none> in the envelope. The specification will be updated in this regard.
2.2	Related sequence – should you not include the previously approved sequence when you start a new regulatory activity?
	No, each Regulatory activity is the start of a new sequence with no related sequence.
2.3	Related sequence - when should the related sequence be included?
	The related sequence number describes the relationship of additional information to the original submission or subsequent submissions within a regulatory activity. *Therefore, it should be included for all sequences subsequent to the original submission in a regulatory activity.* *Refer to the example on the use of the related sequence in 2.21 South African Specification for eCTD Regional - Module1.*
2.4	What submission type should be used in the envelope when responding to a P&A and Clinical recommendation in one sequence?
	The occurrence is currently "unique" and will be changed to "Repeatable" in the next update. Until such time the type "**pre-reg-cr:** Response to Council resolutions" *should be used.*
2.5	It is correct that the way 3.2.R is defined fits into the ICH DTD, but where is it defined?
	The File-Folder Structure & Names are included in the South African eCTD Validation criteria.
2.6	What is the correct file folder structure and names expected in 3.2.R
	The example as in Figure 4 under3.1.6 in guideline 2.23 Submission in eCTD format should be followed. The validation criteria will be updated accordingly. *Documents should be included in node extensions and sub-folders.*
2.7	It is important to check that software vendors can support node extensions as described for 3.2.R
	Noted.
2.8	It was stated that the maximum path length for the folder/file name is 180 characters, but the ICH allows 230 characters. Is the maximum path length of 180 characters only for module 1 or for modules 2 to 5 as well?
	Problems were experienced by other regulators with processing of some sequences provided by applicants because the file path was too long and truncated, either in production of hard media or in manipulation across servers within the agency. The maximum file path length was reduced from 230 characters to 180 by e.g. Swissmedic and EMA. *The 230 characters allowed by the ICH specification include characters for use by the authority. Therefore 180 characters are allocated for use by the applicant for all modules.* *The total file folder path length must not exceed 180 characters. Counting starts from the first digit of the sequence number in the sequence number folder name.*

2.9	Must the Extedo validator tool be used?
	Any validator tool may be used that has been proven to comply with the SA MCC validation criteria.
2.10	Was the naming convention changed in line with ICH, e.g. API changed to Drug Substance?
	The ICH specification and DTD are unchanged for South Africa in terms of technical requirements. Local guidelines refer to content.
2.11	Is the folder structure checked during validation?
	No, folder structure is not checked during validation. In the introduction phase of eCTD we suspended the folder structure check. We plan to introduce this check in the next update of the MCC validation criteria. We highly recommend following the file and folder naming convention with each application to MCC. We reserve a rejection of a submission for non-observance of the file & folder rules based on a business validation rules assessment. This is valid for all modules.
2.12	Which documents must be included as "New"?
	As indicated in the validation template, the operation attribute of the following documents should be reflected as "new": • 1.0 Letter of application • 1.2.1 Application form • 1.2.2.1 Proof of payment • 1.2.2.4 Electronic copy declaration • 1.5.2.1 Tabulated schedule of amendments
2.13	Should documents that have to be included as "New" be placed in node extensions?
	No, node extensions should not be used. Additional descriptive text must be included in the leaf title to assist with identification of specific document (see expectations for leaf titles below).
2.14	What are the expectations for leaf titles?
	Point 3.5 of guideline 2.23 Submission in eCTD format states: "As eCTD viewing tools will display all "new" leaf elements in a current or cumulative view, it is recommended that additional descriptive text be included in the leaf title to assist with identification of specific letters. This will help identify each letter of application leaf and the submission it is in, rather than having the letters named the same in each sequence." *However, this should be applied where the operation attribute is always new or where multiple documents may be included e.g. 1.2.1, 1.7.3, 1.3.1.2* *The leaf titles should be short, meaningful, and indicative of the document's content, so that someone who isn't familiar with the application would know what the document is from the leaf title without having to open the document.*

2.14 cont	*Examples (as seen using an XML viewing tool):* 
2.15	Should hyperlinks be included in the validation template? *Yes, sections B, C and D should be hyperlinked for ease of reference during technical verification by the evaluator.*
2.16	How must "Best practice warnings" in validation be handled? *For any Best Practice criteria that are not met, the applicant must include a justification in the letter of application, the reviewer's guide or in an added note to the submission, e.g. to prevent changing the MD5 checksum.*
2.17	Where must the MD5 checksum be submitted? *The printout of the checksum file (index-md5.txt) should be attached as an annex to the letter (paper version). The annex must be dated and signed. The product name, application number, and relevant sequence must also be indicated.*
2.18	When should bookmarks be included? *Provide bookmarks for documents exceeding 5 (five) pages that contain multiple headings/sections, tables, figures.* *Provide enough bookmarks for easy navigation in the document.* *For documents with a ToC, bookmarks for each item listed in the ToC should be provided including all tables, figures, publications, other references and appendices.*
2.19	Should Tables of Contents include hyperlinks? *If a document has a Table of Contents (ToC) it must be hyperlinked to the corresponding section in the document.*

3 Questions about submission in eCTD format

3.1	Tracking table – must it be included in the letter or separately, and if separately, where and what is the file name?
	It can be in the letter of application or as an annex to the letter. It may be named as such, i.e. Tracking Table.
3.2	Reviewer's guide – must it be included in the letter or separately, and if separately, where and what is the file name?
	It can be in the letter of application or as an annex to the letter. It may be named as such, i.e. Reviewer's Guide.
3.3	Is there a special form or format in which to apply for the application number?
	No, the applicant has to write and submit a letter on the company letterhead, using the working code "eCTD AGC".
3.4	Must the request for an application number be faxed, or can it be e-mailed?
	A letter on a company letterhead with an original signature is required. It should preferably be submitted at Reception for log-in purposes. It may be faxed if arranged with the Director or Deputy-director of Operations & Administration, but not e-mailed.
3.5	How long before submission must applicants request the application numbers(s)?
	Four weeks.
3.6	Which working codes should be used for eCTD submissions, i.e. are there special working codes?
	No, the usual working codes as per the General Information guideline should be used. The working codes should, however, be preceded by eCTD, e.g. "eCTD ANA".
3.7	At what stage should the application fees be paid?
	The screening and application fees must be paid when the initial sequence is submitted and proof of payment included in 1.2.2.1. The fees payable will be indicated in the letter that will be sent with the application numbers.
3.8	If questions are asked, what is the time frame to get answers?
	It will depend on whether the question relates to technical or business aspects.
3.9	How many copies of the CD/DVD must be submitted?
	One, unless otherwise requested.
3.10	Will there be a special e-mail address for eCTDs?
	*Yes, it is ectd@mccza.com and is also provided under Contact the MCC on the MCC website. This address is intended **only** for eCTD-related queries and not for submission of eCTD or other documents.*
3.11	If modules 4 and 5 were submitted electronically before, what will happen to the submission - will it be reviewed as usual or must it be resubmitted as eCTD?
	The submission of Modules 4 and 5 on a laptop for the evaluator is no longer accepted. Modules 4 and 5 were accepted in electronic format for the screening and thus the file copy, if specifically applied for, but at the time MCC reserved the right to ask for paper copies. If the electronic format is not hyperlinked to the PI and between the modules (at least in NeeS format), the applicant may be requested to reformat and resubmit for the file copy for those applications already submitted before 01 April 2016.

3.11 cont.	*The application will be evaluated according to the normal procedure with the post-screening sets (copies for evaluation) submitted in hard copy.* *From 01 April 2016 the eCTD format will be the only electronic format accepted for new applications for registration of New Chemical Entities. Therefore the NeeS format previously accepted for Modules 4 and 5 will no longer be accepted for the file copy.*
3.12	Industry is happy that they no longer have to submit post-screening copies, but will they get confirmation that a product has passed screening/validation?
	Yes, a letter will be sent to the applicant for the first sequence submitted (i.e. 0000). At this stage the applicant will only be notified for subsequent sequences if there are non-compliances.
3.13	How long will CTDs still be accepted after going live with eCTDs?
	No deadline has been set yet. eCTDs will be the preferred way, but especially small companies cannot be forced to convert. Five years were given to convert to CTD – due date 01 June 2016.
3.14	Will eCTDs go into a faster queue?
	Due to more efficient processes, the entire registration process should be quicker for eCTDs.
3.15	Will MCC provide a list of preferred software vendors?
	No, applicants are free to choose any software vendor, provided that the eCTDs will comply with the prescribed requirements.
3.16	Can a submission on the CD-Rom or DVD be compressed?
	The data on the media should not be packed into a zip-file, rar-file or any other file format that has been compressed.
3.17	Which documents are mandatory for all application types.
	The letter of application (1.0), application form (1.2.1) and validation template (sections as indicated on the template).
3.18	What is the expectation of the electronic copy declaration?
	This must be submitted in 1.2.2.4 and as it is a declaration, it must be signed and dated and indicate the relevant sequence.
3.19	Are scanned signatures allowed in Module 1?
	Yes, but the scanned documents must be searchable, i.e. OCR scanned.
3.20	Which headers and footers may be included in the eCTD?
	The requirements for documentation as for the ICH eCTD apply. *"The M4 Granularity document specifies that all pages of a document should include a unique header or footer that briefly identifies its subject matter. With the eCTD there is a significant amount of metadata available to the reviewer to allow easy identification of the document but it is still appropriate to have a unique identifier on each page (header or footer) of the document (e.g., when the document is printed or multiple documents are viewed on screen at the same time). The unique identifier does not necessarily have to contain the CTD section identifier or other metadata. It should be sufficient to identify the general subject matter of the document (e.g., study identifier, batch number)."* *Footers of the official forms, e.g. Modules 1.2.1, and validation template, may not be changed.*

4 Update History

Date	Reason for update	Version & publication
April 2013	First publication	v1 May 2013
Feb 2016	Update following questions asked in the pilot phase	v2 February 2016
Feb 2016	Clarification of requirements - 2.13 (new), 2.14, 3.3, 3.6 (new), 3.7 (new), 3.11, 3.20 (new)	v2-1 April 2016