SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

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 CEO and the website.

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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
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
MCC	Medicines Control Council
P&A	Pharmaceutical and Analytical
PI	Professional Information
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
Q&A	Question and Answer documents
SAHPRA	South African Health Products Regulatory Authority
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 a summary of questions that relate to the South African guideline, validation criteria and specification documents (i.e. 2.21 South African Specification for eCTD Regional - Module1, 2.22 South African eCTD validation criteria and guideline 2.23 Submission in eCTD format) and represents the South African Health Products Regulatory Authority's current view.

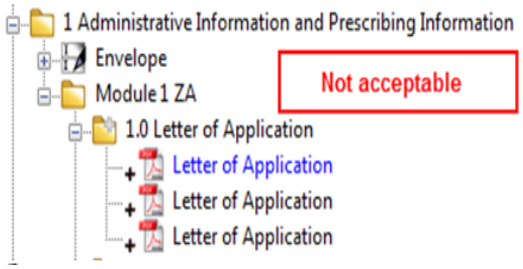
It is intended to be a dynamic document that supplements and actualises the above-mentioned guideline documents. The document will be updated as the guideline documents undergo change control or as new questions are submitted to the Authority.

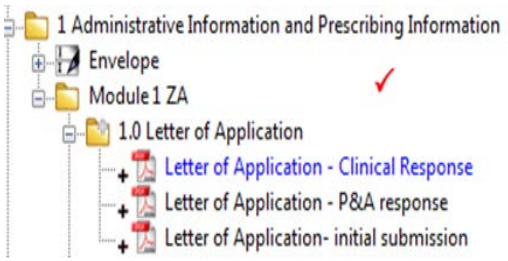
In addition, further eCTD Q&A issued by ICH and relating to all regions can be found at http://estri.ich.org/eCTD/index.htm.

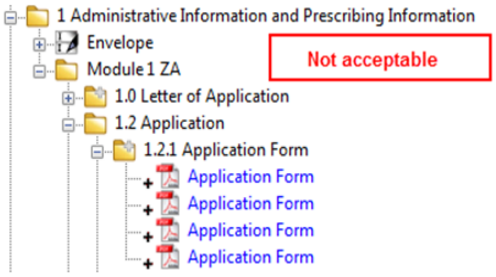
2 Questions about the Technical Requirements

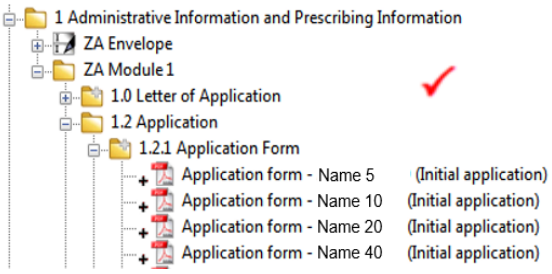
2.1	Related sequences – must it be left open, or must <none> be included similar to Swiss?
	When a new Regulatory activity is started and there is no related sequence, the related sequence should be indicated as <none> in the envelope. The specification has been updated in this regard.
2.2	Related sequence – 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 has been changed to "Repeatable". Both types should be included, e.g.: • **pre-reg-pa**: Pharmaceutical and Analytical • **pre-reg-cl**: Clinical .
2.5	It is correct that the way 3.2.R as 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. See also guideline 2.23 Submission in eCTD format.
2.6	What is the correct file folder structure and names expected in 3.2.R
	The example as in Figure 4 under 3.1.6 in guideline 2.23 Submission in eCTD format should be followed. The validation criteria have been updated accordingly. This became mandatory on 01 May 2017. *Documents should be included in node extensions and sub-folders. Incorrect structure and granularity may lead to business validation failure.*

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 SAHPRA 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?
	Yes, folder structure will be checked during validation in accordance with the amended validation criteria, which became mandatory on 01 May 2017. We highly recommend following the file and folder naming convention with each application to SAHPRA. 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 and point 5.4 of guideline 2.23 Submission in eCTD format, 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, additional descriptive text has to 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."

<table>
<tr><td></td><td>
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
Leaf titles are an important part of eCTD submissions as they are displayed to the evaluator when evaluating an eCTD application. Including meaningful information in leaf titles makes submissions easier to navigate and makes evaluators' jobs easier.
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.
Leaf titles should be suitably descriptive for the current sequence and all possible life-cycle sequences.
Examples (as seen using an XML viewing tool):








</td></tr>
<tr><td>2.15</td><td>What is the difference between a leaf title and a file name?</td></tr>
<tr><td></td><td>
Both the PDF file name and the leaf title are used to identify and describe each file in the eCTD. The leaf title does not have to be the same as the PDF file name given to the file.
The PDF file name is seen if navigation through the dossier is done via a direct view of the files and folders.
The leaf title is displayed / seen if the XML backbone and stylesheet or a dedicated eCTD review tool is used to navigate through the submission. Attention should be given to 2.14 above in terms of leaf title expectations to ease navigation through eCTD submissions.
Examples:
<table>
<tr><td>File name:</td><td>Leaf title:</td></tr>
<tr><td>application-letter.pdf</td><td>Letter of application (Initial application)</td></tr>
<tr><td>Application-form.pdf</td><td>Application form 10 mg initial application</td></tr>
<tr><td>pi.pdf</td><td>Proposed Professional Information initial application</td></tr>
<tr><td>avail.pdf</td><td>Comparative dissolution study report</td></tr>
</table>
</td></tr>
<tr><td>2.16</td><td>Should hyperlinks be included in the validation template?</td></tr>
<tr><td></td><td>Yes, technical sections should be hyperlinked for ease of reference during technical verification by the evaluator. This has been included in the validation criteria, which became mandatory on 01 May 2017.</td></tr>
</table>

2.17	How must "Best practice warnings" in validation be handled?
	For any Best Practice criteria that are not met, the applicant must add a note to the submission in paper with a justification for the warnings.
2.18	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.
2.19	When should bookmarks be included?
	Provide bookmarks for documents exceeding 5 (five) pages that contain multiple headings/sections, tables, figures in all modules. *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.* *Refer to the Guidance for submission of regulatory information in eCTD format.*
2.20	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.
2.21	How do I ensure that thumbs.db files are not created on the CD/DVD that I submit to the Authority?
	Once the submission is ready in your export folder and you want to check something, do not open any files, but make a copy somewhere else and check there. *Also refer to the Guidance for submission of regulatory information in eCTD format, section 4.10*
2.22	What does it mean when the "export" of the submission is referred to?
	This is equivalent to "create" or "publish" the eCTD
2.23	Are hyperlinks checked during validation of the submission?
	Yes, refer to the current SA eCTD validation criteria for the technical as well as Best Practice criteria.
2.24	Should published references which are included in Modules 4.3 and 5.4 be text searchable?
	If these references are used to support the indications claimed for the application, and are cross-referenced in the package insert, they would have to be text searchable (OCR scanned). The EMA guidance for industry on providing regulatory information in electronic format, version 4.0 of April 2016[1], includes a very useful guidance on text searchable documents in Annex 2, which could be used at this stage.

[1] http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v4%200-20160422-final.pdf

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. Its location can be facilitated by including a bookmark when included as an annex to the letter. *Note that if a tracking table is submitted as a separate document, it has no lifecycle and should therefore always be submitted with the document operation attribute "new". This separate document is not recommended due to the increase in number of documents in this section. Rather include as annex to the letter.*
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. Its location can be facilitated by including a bookmark when included as an annex to the letter. *Note that if a Reviewer's guide is submitted as a separate document, it has no lifecycle and should therefore always be submitted with the document operation attribute "new". This separate document is not recommended due to the increase in number of documents in this section. Rather include as annex to the letter.*
3.3	Is there a special form or format in which to apply for the application number?
	No, the applicant has to send a written request on the official company letterhead to the Authority for the attention of Operations & Administration with details of the application(s) to be submitted, using the working code "eCTD AGC". *The proposed proprietary names should be indicated.* *The type of data to be submitted in support of safety and efficacy should also be indicated.*
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 Document Reception for log-in purposes but may be e-mailed to the eCTD link on the website.
3.5	How long before submission must applicants request the application numbers(s)?
	Eight weeks. Allow four weeks for allocation of numbers.
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 (validation) 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 number/s.
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	How must the CD/DVD be submitted?
	This should be submitted in an appropriate envelope/sleeve, attached securely to the paper documents, preferably on top, that can be easily accessed. Stapling of an envelope to the letter or submitting in a separate, loose envelope is not advised.
3.11	Will there be a special e-mail address for eCTDs?
	*Yes, it is ectd@mccza.com but is soon to change and is also provided under Contact the Authority on the website. This address is intended **only** for eCTD-related queries and not for submission of eCTD or other documents. Two addresses will be supplied – one for the request for application numbers, and the other for technical queries.*
3.12	How will committees' recommendations be received?
	Committees' recommendations are co-ordinated in the eCTD office in Ops & Admin. The recommendations will be e-mailed to the applicant when all the relevant committees' recommendations have been received, to allow for submission of a response with one timeline and in one sequence. Recommendations should not be sent to the applicant directly from an evaluation unit. The applicant should inform the eCTD office, e.g. via the eCTD link on the website, if this should occur in error.
3.13	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 (now SAHPRA) 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.* *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 is the only electronic format accepted for new applications for registration of New Chemical Entities and from 01 January 2017 for generics. Therefore the NeeS format previously accepted for Modules 4 and 5 will no longer be accepted for the file copy.* *However, with the Backlog Project eSubmissions that are not eCTD will be accepted for an interim period. Please refer to the new eSubmission guideline to be published shortly.*
3.14	Is a screening copy required as for paper CTD submissions
	No, there is no separate screening submission for eCTD. Screening (validation) and application fees are paid with the initial submission. Compliance with all screening/validation requirements results in the submission being ready for evaluation without "post-screening" copies being submitted as for paper submissions.

3.15	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. Due to the delay caused by the industrial action and then the relocation to the CSIR campus, business validation outcome letters will not be issued routinely. Unless critical business validation issues are identified, these will be included with the first evaluation recommendations.
3.16	Where must the copy of the Authority's letter with the validation outcome be included?
	If submitted in section 1.8 it should be submitted as an annex to the validation template, indicated with a bookmark. *Alternatively, it should be submitted as an annex to the letter of application in section 1.0, indicated with a bookmark. Note that if it is submitted as a separate document, it has no lifecycle and should therefore always be submitted with the document operation attribute "new".* *As with the other communications in section 1.0, this separate document is not recommended and the bookmarked annex is preferred.*
3.17	How long will CTDs still be accepted after going live with eCTDs?
	SAHPRA will only be accepting digital submissions from the go-live of the Backlog Project. eCTDs will be the preferred way, but especially small companies cannot be forced to convert. If a valid reason can be provided, eSubmissions will be accepted for a limited period of time.
3.18	Will eCTDs go into a faster queue?
	Due to more efficient processes, the entire registration process should be quicker for eCTDs.
3.19	Will SAHPRA 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.
3.20	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.
3.21	Which documents are mandatory for all application types.
	The letter of application (1.0), application form (1.2.1), electronic copy declaration (1.2.2.4) and validation template (1.8) (sections as indicated on the template). *However, the application form, electronic copy declaration, and validation template are not required for a close-out submission if an application is withdrawn or the registration is cancelled.* *Refer to the validation criteria rules 9.3, 9.4 and 9.5*
3.22	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.. The specific documents submitted in hard copy in addition to the eCTD have to be listed. The document has to be identifiable, i.e. indicate the applicant, product name and application number, and relevant sequence.

3.23	Are scanned signatures allowed in Module 1?
	Yes, but the scanned documents must be searchable, i.e. OCR scanned. The paper copies have to reflect the original signatures, not scanned signatures.
3.24	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. MS Word versions without the field for file name in the footer are available on the SAHPRA website.*
3.25	Can I submit my eCTD on a re-writable DVD-RW or CD-RW?
	Yes, but the Burning Session must be closed. However, the use of re-writable disks is not encouraged as an ISO copy cannot be made.
3.26	Which application number do I have to fill in the envelope, when I file a line extension?
	All application numbers have to be listed in the envelope. In the letter of application a clear reference has to be made to which originally issued application number this line extension belongs. The first issued application number for a product line is the identifier for the eCTD application.
3.27	What happens if I have a delay in my submission and cannot submit my application within the 4 weeks after issuing of the application number?
	Just notify the Director or Deputy-director of Operations & Administration about the delay and the application number stays valid for that particular year.
3.28	Must I include the registration number in the envelope when I submit amendments for a registered product?
	No, the application number, which is the eCTD identifier, must still be used.
3.29	In which format should application numbers be included in the envelope when the eCTD pertains to more than one product or product strength, i.e. 470001/2, or 470001, 470002 or as separate elements?
	Application numbers must be included as separate elements, e.g. *470001* *470002*
3.30	In which format should proprietary names be included in the envelope when the eCTD pertains to more than one product or product strength?
	Proprietary names must be included as separate elements, e.g. *Name 10 mg* *Name 20 mg*

3.31	Must I submit a sample with the screening copy?
	There is no "screening copy" as for paper submissions. A sample of the smallest pack size has to be submitted with sequence 0000 for new applications for registration. The application number should be indicated on the labelling, as it would already have been allocated, for ease of identification. *If the sample is small enough to be submitted in an envelope, this should be attached to the front of the submission to allow for easy removal.*
3.32	When should the registration fee be paid?
	The registration fee may be paid and proof of payment included when the applicant submits the final responses to Authority recommendations, to prevent submission of an entire sequence just for the proof of payment of the registration fee.
3.33	Where must I submit the comparability report for an application for registration of a biosimilar?
	At this stage this report should be submitted in Module 3.2 R.8 Other
3.34	How and where should the proposed, annotated and clean versions of the professional information (PI) and patient information leaflet (PIL) be included?
	New submissions: *Include the proposed and cross-referenced PI in 1.3.1.1 and the proposed and cross-referenced PIL in 1.3.2.* ***Response to pre-registration Authority recommendations:*** *Include the amended, annotated versions of the PI and PIL in 1.5.5 as 2 separate documents. The clean versions of the amended PI and PIL replace the versions in 1.3.1.1 and 1.3.2 respectively.* ***Post-registration amendments****: Replace the previous amended and annotated versions in 1.5.5 with the updated, annotated and cross-referenced versions in 1.5.5. There is no need to resubmit the currently approved versions of the PI and PIL – a reference/hyperlink to the approved versions in the previous sequence is sufficient.* ***Response to post-registration recommendations:*** *Replace the versions of the PI and PIL in 1.5.5 with the new, amended, annotated versions. The clean versions of the amended PI and PIL replace the versions in 1.3.1.1 and 1.3.2 respectively.*
3.35	Where must a PSUR be submitted?
	This should be submitted in module 5.3.6
3.36	Should a request for a section 36 exemption be submitted in the eCTD as a new sequence?
	This will depend on the type of exemption applied for (once-off or permanent), and will be handled on a case-by case basis. It should therefore be discussed with the eCTD office.
3.37	Should a request for a once-off amendment be included in the eCTD as a new sequence?
	At this stage it should be handled outside of the eCTD, as it is supposed to be a once-off occurrence only and should not affect the lifecycle of any of the approved documents in the eCTD. Paper copies of any sections referred to will have to be submitted.
3.38	Where must the SCoRE document be included
	This document should be included in Module 2.2 Introduction, as a separate document with the leaf title "SCoRE document", as it will have its own life cycle.

3.39	How should the application for registration of a clone be handled?
	Please also refer to the latest version of the guideline 2.23 Submission in eCTD format. *The letter applying for the eCTD identifier should clearly indicate the original application upon which the clone is based.* *For an existing eCTD of a registered product, the clone should be submitted similar to a duplicate application.* *The letter of application, M1.2.1, 1.2.2.1, 1.2.2.4, labelling (1.3.1.1, 1.3.2, 1.3.3) reflecting the proposed proprietary name as [PRODUCT NAME] and 1.5.3 reflecting all proprietary names should be submitted. (This is apart from the MD5 checksum and validation report.)* *The name/s and application number/s of the clone/s should be included in the envelope under Multiple/Duplicate Applications.* *Where the original application for registration is still in paper format, a submission in eCTD format will be required as for a baseline submission, as sequence 0000. The application for the clone will then be sequence 0001.* *Include copies of the latest letters of* • *approval of any amendments to the registered product, including the PI and PIL,* • *the allocation of the shelf-life of the product and* • *the allocation of the retest period of the API/s* *as bookmarked annexes to the letter of application in section 1.0* *At this stage different strengths should be combined into one dossier, with the first application number being used as the eCTD identifier.*

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
Sept 2016	Updated due to amended validation criteria, technical and guidance documents	v3 November 2016
May 2019	Change from MCC to SAHPRA – 1, 2.9, 3.19, 3.24, 3.32, 3.34 Changes to Abbreviations & Acronyms Changes to 2.4-6, 2.11, 2.14, 2.16, 3.1-5, 3.7, 3.11, 3.13, 3.15, 3.17, 3.21-23, 3.27 Added 2.15, 3.10, 3,12, 3.14, 3.16, 3.30-31, 3.38, 3.39.	v4 May 2019