Central Administration of Pharmaceutical Products
General Administration For Human Pharmaceuticals Registration

Central Administration for Biologics, Innovative Products, and Clinical Studies
General Administration of Biological Products
General Administration of Innovative Products

Technical Guidance for eCTD Submissions in Egypt

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1 Introduction

This guidance document is intended to assist pharmaceutical companies with the submission of regulatory information in electronic Common Technical Document format (eCTD) to the Egyptian Drug Authority (EDA).

The eCTD format is mandatory to use for all regulatory submissions within all procedure types for Egypt.

This document is an important guidance for the use of eCTD in Egypt and may be regularly updated in the light of changes in national Egyptian legislation and agreements with EDA. If needed, there are also Q&A documents published in between versions of this guidance as a response to change requests or new requirements to be addressed. Other relevant information about eCTD and electronic submissions can be found at the EDA eCTD Website.

1.1 Glossary

A brief glossary of terms (for the purpose of this document only) is indicated below:

Term	Definition
Applicant	The authorized person or company who submits an application for marketing authorization of a new medical product, an update to an existing marketing authorization or a variation to an existing marketing authorization.
Applicant's Information	Regulatory information submitted by an ***applicant*** to obtain or maintain a marketing authorisation that falls within the scope of this guidance document.
Active Substance Master File holder	The company who is the legal owner of Active Substance Master File as documentation of the manufacturing of an active substance.
Baseline Submission	A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of the latest approved valid documents that have already been provided to the authority but in another format.
DTD	A set of rules that defines the structure, elements, and attributes allowed in an XML file. In eCTD, XML files describe the organization, metadata, and relationships of submission documents. The DTD acts like a blueprint, telling both the applicant's publishing tool and the regulatory authority's receiving system exactly how the XML must be formatted and what elements are valid.
eCTD application, also known as a dossier	A collection of electronic documents compiled by a pharmaceutical company or its agent in compliance with Egyptian legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An ***eCTD application*** may comprise a number of ***regulatory activities***. For products with different dosage forms and strengths are submitted under separate applications.
Envelope	Part of the eg-regional.xml file containing high-level metadata about the submission package. See section 3.2.2Error! Reference

	source not found.
High Level Number	**Submission Number** This number represents the high-level procedure number related to the regulatory activity in case of submissions of grouped variations if multiple products are concerned. Samples are provided in the EG M1 Specification. Note: not required in case only one product is concerned. Issued by EDA through the portal.
Non eCTD Submission format	Non eCTD Submission format includes any electronic submission including CTD submission that are not in an eCTD format.
Procedure Tracking Number	Unique identifier assigned to the application procedure. Issued through the EDA portal.
Regulatory Activity	A single sequence or a collection of sequences covering the start to the end of a specific business process, e.g. an MAA application or Variation. To allow a more precise handling, the regulatory activity will be classified using a controlled vocabulary (submission type or regulatory activity type) and a free text field for a short narrative description.
Sequence	A single set of information and / or electronic documents submitted at one particular time by the applicant either as a part of or as the complete application. Any collection of content assembled in accordance with the eCTD specification (ICH and EG) is described using metadata as defined by the EG envelope. Sequences may be related to one another within one regulatory activity. The related sequence number should always be stated. In case of activities with only one sequence the same sequence number is used.
Submission Type	The submission type describes the regulatory activity to which the content is submitted.
Submission Unit Type	The submission unit type element of the envelope metadata set describes the content at a lower level (a “sub-activity”) which is submitted in relation to a defined regulatory activity such as the initial submission, the applicant response to validation issues or list of questions or any other additional information.

Working Documents	Working-documents folder can be added to a submission for documents requested by the authority these documents should be placed outside the eCTD structure and named for example 0000-workingdocuments. The working document folder can be included in the zip file at the top-level structure for example 0000 and 0000-workingdocuments would be the two folders in the zip file.

2 General Considerations

2.1 Scope

2.1.1 Types of Products

This guidance covers the submission of electronic regulatory information for all human medicinal, biological and innovative products falling within the competence of EDA. This includes, but is not limited to, both prescription and over the counter medicinal product. The product types include for example small molecules, biotech products, vaccines, blood products or ATMPs.

2.1.2 Types of Submission

This guidance applies to all submissions related to the authorisation and lifecycle of medicinal products, for example: new marketing authorisations, variations, renewals, Active Substance Master File (ASMF), Plasma Master Files (PMF) and withdrawals. (refer to Annex 6 for the full list of submission types)

2.1.3 Types of Submission Units

The submission units allow sequences that make up a Regulatory Activity to be grouped together. It describes the submission steps within a Regulatory Activity, such as initial, validation-response, and response in case of a new MAA.

The submission unit ‘additional-info’ should be used for additional information (which could include, for example, missing files) and should only be used when ‘validation-response’ or ‘response’ is not suitable.

The submission type ‘corrigendum’ should only be used in exceptional circumstances to correct information after the Regulatory Activity has concluded. Its use must be discussed and agreed with EDA in advance on a case-by-case basis.

2.2 Structure of Submissions

This document provides guidance on how to organise application information for electronic submission using the eCTD specifications. Guidance on the detailed information to be included is described in the Common Technical Document (CTD), and relevant ICH guidelines.

The structure and organisation of an eCTD submission is defined by the following standards:

- ICH M2 eCTD Specification
- EG eCTD Module 1 Specification
- Relevant ICH guidelines

Annex 1 contains links to the currently approved version of these documents and other useful references.

For EDA, the applicant should submit one eCTD per strength or dosage form, and it is expected that each of these eCTD applications will be maintained individually, such that submission of a single sequence that covers more than one strength or dosage form will not be possible.

This means a separate eCTD lifecycle for each strength or form of a product, and all submissions must be provided for each eCTD separately.

2.3 Transitional Arrangements

The specifications mentioned in Section 2.2 above are likely subject to changes and are likely to affect both eCTD building tools and the applicant's internal business processes as well as the Authority's review tool and processes. Once a new eCTD specification and/or the related validation criteria have been approved, eCTD building tools will need to be updated accordingly, and specific transitional guidance will be provided on each occasion. However, minor changes that do not change the Document Type Definition (DTD) of the eCTD specification, but only the text may also be published and would then not affect any tools, but rather the handling or business process of the eCTD lifecycle.

Please note that it should not be necessary to reformat and resubmit previously submitted applications to reflect such changes.

2.4 Change to eCTD Format

eCTD is the mandatory format for all electronic submissions referred to in 2.1. If the product dossier was earlier handled in paper or Non eCTD Submission format, the next upcoming submission for a new regulatory activity needs to be submitted in eCTD format.

This does not include submissions concerning other ongoing regulatory activities related to that eCTD application (e.g. responses to questions to ongoing variations), in which case, they must be completed in the format that they started in before transitioning to eCTD.

If the dossier has already been provided in Non eCTD Submission format, the applicant should submit the new data in eCTD format starting the lifecycle in accordance with eCTD specifications. The first submission in eCTD format will normally be sequence 0000, even if sequential numbers were used for the Non eCTD Submission format. For clarity, the cover letter should always explicitly state that the submission involves a switch to eCTD format. As the documents already exist in an electronic format, it would be preferable to first re-send the currently valid documents, as a baseline eCTD dossier in sequence number 0000 and then the first new regulatory activity as 0001. Please see Section 2.11 for further information on the content of baseline applications and the acceptability of scanned documents.

In any case, a tracking table is essential to understand the sequencing of your eCTD submission and should be included in all submissions in all procedure types (please refer to Section 3.2.3).

A baseline submission is required at the time of changing to eCTD to give the agencies access to all or at least part of the previously submitted documentation within the eCTD lifecycle (see Section 2.11.).

2.5 General Submission Considerations

2.5.1 Document Granularity

Submissions are a collection of documents, and each document should be provided as a separate file. The detailed structure of the eCTD should conform to the ICH Granularity Document and EG M1 specification. Careful consideration is needed when deciding the level of Module 3 granularity (please refer to Annex 3,)

2.5.2 File Naming

The eCTD file naming conventions described in the ICH M2 eCTD Specification and EG Module 1 eCTD Specification are highly recommended as best practice. If an applicant wishes to submit multiple files in one section, where only one highly recommended name is available, this can be achieved by using a suffix to the filename, such as using the file name-var.pdf convention as described in the EG Module 1 eCTD Specification (e.g. pharmaceutical-development-container.pdf). The variable part of the name must not contain “illegal” characters (e.g. %, /, <).

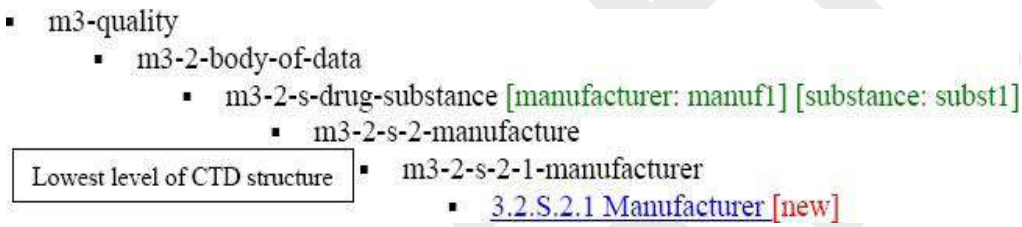
File names, including the extension, must not exceed 64 characters. Also, the folder names must not exceed 64 characters, and the total file folder path length must not exceed 180 characters. Counting starts from the first digit of the sequence number in the sequence number folder name.

For further guidance on file naming, please refer to the “File-Folder Structure & Names” work sheet included in the current validation criteria

2.5.3 Placement of Documents

Guidance on the placement of documents within the eCTD structure can be found in EG eCTD M1 Specification.

In the submission structure, leaves should typically be placed at the lowest level of the CTD structure, although there are some exceptions to this guidance, for example, in 32p4-contr-excip, where the files excipients.pdf, excipients-human-animal-var.pdf or novel-excipients-var.pdf can be placed alongside folders containing details of other excipients. The lowest levels of the CTD structure (including node-extensions) must contain at least one leaf, although this should normally be managed automatically by the eCTD building tool.



Every leaf must have a value for the 'title' attribute.

2.6 Correspondence

The eCTD is designed to ensure that users have a current view of the information submitted in the appropriate place of the dossier at all times. Therefore, formal responses to questions should always be submitted in eCTD format, as well as any correspondence that relates directly to the content of the dossier.

2.7 Paper Requirements

In addition to the eCTD, EDA requires the following documents to be submitted in hardcopy to support the application:

1. Legalised CPP
2. Labelling documentation (Outer & Inner Pack, SmPC & PIL)

Please refer to the guidelines on the EDA eCTD webpage for further information.

2.8 Hardware

EDA will not accept any hardware (laptops, desktops, external hard drives etc.) from applicants in connection with the submission of information in electronic format. The electronic

information should be directly submitted using EDA's eCTD Portal (https://reg-submit.edaegypt.gov.eg).

2.9 General Technical eCTD Information

2.9.1 Identifier for Applications

To help enable archiving the sequence with the correct dossier (eCTD lifecycle), applicants must state a unique identification of the dossier in the form of a UUID. The identifier must be defined with the first sequence of a new dossier, and it must be consistent throughout the eCTD lifecycle. The identifier must not be changed except in certain scenarios, see Section 2.11.2.

The UUID is a 32-digit (8+4+4+4+12) hexadecimal string, for example: "123e4567-e89b-12d3-a456- 426655440000". When defining a UUID the string should be decided at random. The string should contain no information referring to any other metadata. This is to ensure consistency even if the relevant metadata should change. The chance of two different dossiers having the same UUID is next to none if the UUIDs are truly defined at random.

2.9.2 File Formats

Generally, the recommended file format for content documents is PDF however, in specific cases, other formats will be exceptionally accepted in the eCTD modules. All PDF files included in an eCTD (irrespective of the module) should be versions 1.4, 1.5, 1.6, 1.7, PDF/A-1 and PDF/A-2 except where there is an agency-specific requirement for a later version (e.g. for an application form).

For the latest acceptable file formats list, please refer to the document "EG Accepted File Formats for eCTD". This document provides details on which file formats are exceptionally allowed within eCTD submissions in EG. It is a list of accepted file types and the eCTD locations in which those file types should be provided.

Unless specifically requested, the documents should only be provided in one format, once in the life cycle (hence, only once in the sequence).

These file formats should not be embedded within a PDF file but submitted as standalone files. Other formats (not specified in the document) for Module 1 content provided outside of the eCTD in the working-documents folder should be used as required by the receiving authority.

For data requested by authorities which needs to be provided in any other format than specified above, please follow the instructions given by requestor.

Files that might be requested by EDA in MS Word format in addition to the PDFs should not be included in the eCTD structure (refer to 2.9.10) but be provided in the working documents

folder. Further detailed guidance on file formats can be found in the ICH eCTD specification document and EG Module 1 specification.

2.9.3 Portable Document Format (PDF)

Portable Document Format (PDF) is an ISO standard (ISO 19005-1:2005 Document management – Electronic document file format for long-term preservation – Part 1: Use of PDF 1.4 (PDF/A-1) and ISO 32000-1:2008 Document management – Portable document format – Part 1: PDF 1.7). Although created by Adobe Systems Incorporated, there are several alternative suppliers of PDF software. Applicants need to check that their PDF documents meet the following key requirements:

- PDF version 1.4, 1.5, 1.6 or 1.7 should normally be used, except where there is an EG requirement for another version.
- PDF/A format is recommended where possible.
- PDF 1.3 or earlier versions are not acceptable for technical reasons. No exceptions will be made. For example, if a literature reference is received in PDF 1.3 or earlier, then the applicant must convert it to PDF 1.4, 1.5, 1.6 or 1.7, either electronically or by scanning.
- Applicants are requested to ensure that all submissions contain the maximum amount of text searchable content to facilitate the assessment of the eCTD content. PDF documents should therefore, wherever possible, be produced from a text source such as MS Word. If scanning is unavoidable, it should normally include OCR. However, there are some documents where the scanned document would not be expected to include OCR, i.e.:

  - Any GMP certificate
  - Any certificate of analysis
  - Any manufacturer's licenses
  - Any certificate of suitability
  - Any Manufacturing Authorisation
  - Any document written in a foreign language where a translation is provided in English (however, the translation should be text searchable)
  - Any literature references sourced from journals, periodicals and books (except when these are used in a bibliographic application to support the main claims of the application).
  - The blank CRF in a Clinical Study Report
  - Patient data listings (when supplied)
  - CRFs (when supplied)
  - Any page with a signature that does not contain other information key to the understanding of the submission (However, applicants should consider providing signatures on pages separated from key text pages in reports, overviews, etc.)

Additionally, the following requirements should be taken into consideration:

- The fonts used in the PDF should be embedded in the PDF where possible.
- Rendition to PDF should preferably create documents which are" tagged".
- Use 'Fast Web View' where possible to ensure optimum performance of the review system.
- PDFs should not be included in the eCTD as a PDF Portfolio.

Additional details on PDF, including those relating to the good presentation of tables, can be found in the ICH eCTD Specification, Appendix 7. Refer also to the ICH M2 recommendations.

2.9.4 Sequence Numbers

Sequence numbers are used to differentiate between different submissions of the same application over the lifecycle of the product. The review tool being used by EDA can handle sequences submitted out of numerical order, i.e. 0003 submitted after 0004. This can occur when the preparation of a sequence is delayed. However, it is recommended that sequence numbers follow the order of submission of the sequences, as sometimes a higher sequence is technically related to the previous – not yet submitted – sequence which will result in technical invalidation. A Sequence Tracking Table should always be included in section 1.0 in every submission for all procedures. For details see Section 3.2.3.2.

The initial eCTD lifecycle submission should normally have a sequence number of 0000, even if sequential numbers were already used for a Non eCTD Submission format of the same product. If applicants consider that there are good reasons to use another number, they should explain this in the cover letter.

When additional information is submitted in response to questions or when information in a previously submitted sequence is modified in any way, the sequence number of the submission will advance accordingly, e.g. 0001, 0002, etc.

In the case of a technically invalid submission, the same sequence should be resubmitted (unless the recommendation from EDA is different) using the same number (e.g. the initial sequence "0000" will be replaced by another "0000"), after the technical validation findings were fixed. For submissions to the EDA, it is mandatory to use the EDA Portal. If the eCTD is technically valid but needs to be updated due to content/regulatory validation, any revised content should be provided with a new sequence number and the changes clarified in the cover letter.

2.9.5 Related Sequence

All submissions need to contain a value for "related sequence". If the submission unit type is 'initial' or 'reformat' then the related-sequence attribute must have a value equal to the current sequence.

If the submission unit type is not 'initial' or 'reformat', then the entry for related sequence should be populated with the number of the sequence that started the regulatory activity.

Therefore:

- When submission unit = initial or submission_unit = reformat, then the related sequence number always = sequence number and vice versa
- When the submission unit ≠ initial or the submission_unit ≠ reformat, the related sequence always < sequence number.

See below some illustrative examples.

Table 1: Example of a Variation

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0008	Variation to Add a New Manufacturing Site	var-pac-II	0008	initial
0009	Additional supporting document	var-pac-II	0008	validation- response
0010	Responses to Questions	var-pac-II	0008	response

It is expected that there is just one Related Sequence, but there are occasions where more than one Related Sequence should be provided as for example:

When there are two parallel variations (sequence 0002 and sequence 0003) and there is a sequence (0004) that brings the label up to date by including the changes made in both variations.

On these occasions multiple related sequences are used, but if a subsequent sequence relates to only one of the original regulatory activities, then only the related sequence for that particular regulatory activity should be used.

If the related sequences refer to both a single and grouped variation, the metadata should state 'grouped' as being the highest level of regulatory activity.

Further examples are provided in the EG eCTD M1 Specification document.

2.9.6 Leaf Lifecycle Operation Attributes

The leaf lifecycle operation attributes, as stated in the eCTD specification, are 'new', append', replace' and 'delete'. However, in EG, it is recommended that applicants avoid the use of 'append' due to the potential for increased lifecycle complexity.

Lifecycle operations where the leaf targeted by the modified file is in a different CTD section are not allowed. This applies across all the modules of the CTD and is not specific to either the regional or ICH Modules.

Where elements are repeatable, both the element itself and the attributes that define a different position in the table of contents, must be identical when modifying a leaf element in a previous sequence.

Where node extensions are allowed, the node extension title element should be identical when modifying a leaf element in a previous sequence.

Table 2: Repeatable Elements and Attributes that Define Different Sections

Element	Attributes also identifying a section
Module 2	
m2-3-s-drug-substance	Substance manufacturer
m2-3-p-drug-product	product-name dosage form manufacturer
m2-7-3-summary-of-clinical-efficacy	indication
Module 3	
m3-2-s-drug-substance	substance manufacturer
m3-2-p-drug-product	product-name dosage form manufacturer
Module 5	
m5-3-5-reports-of-efficacy-and-safety-studies	indication

Note, in the eCTD XML, sections, leaves and node extensions may have other attributes, such as xml:lang, font-library, version, keywords, ID etc. These attributes, if supplied, do not result in a

new logical section in the eCTD table of contents and therefore lifecycle between leaves where these attributes are not identical is allowed; only the attributes in the table above define different eCTD sections.

Examples:

Pass/Fail Criteria

- A leaf to be submitted in m4-2-2-5 in Sequence 0012 cannot replace/delete a leaf submitted in m4- 2-2-2 of Sequence 0010.
- A leaf in m1-responses cannot modify content in m1-0-cover (different section)
- A leaf in m3-2-s-drug-substance [manufacturer: abcd] [substance: xyz] cannot modify content in m3- 2-s-drug-substance [manufacturer: other] [substance: xyz], or any section other than the specific manufacturer ‘abcd’ and substance ‘xyz’ section.
- A leaf in m1-3-pi with the specific attributes <pi-doc xml:lang="en" type="combined" country="eg"> cannot modify a leaf with different attributes, such as <pi-doc xml:lang="ar" type="other" country="eg">.

Best Practice Criteria

- A leaf in a node extension should only be modified by a leaf in the same equivalent node extension in a subsequent sequence. For example, a leaf in a node extension in m5-3-5-1 of sequence 0000 with a <title> attribute ‘Study 1234’ should not be modified by a leaf in a different node extension with a <title> attribute ‘Study 1234 – update’ in sequence 0001 – the append/replace/delete leaf ideally needs to be in an identical node extension in 0001 (‘Study 1234’ in the same location, m5-3-5-1).

If the applicant places content in the wrong CTD section and needs to correct this (either upon request from the agency receiving the eCTD or because they wish to correct the mistake) then the way to do this is to create two leaf elements in a subsequent sequence. The first leaf will use the “delete” leaf operation to remove from view the incorrectly placed content. The second leaf will usually use the “new” leaf operation to locate the content in the correct CTD section. The file does not need to be resubmitted, the “new” leaf can use the xlink:href attribute to point to the originally submitted content in the earlier sequence.

However, applicants cannot submit a dossier using the old specification and DTD. Therefore, deleting the content in the old section will involve lifecycle from the changed section (for example, m1-additional-data) deleting content in the equivalent section with the original name (in this example, m1-additional). This may not be possible in all eCTD building tools, and if so, applicants are advised to leave the original content as it is, but to start providing new or replacement content in the revised section.

Note: Lifecycle operations across eCTD applications are not allowed.

2.9.7 Bookmarks and Hypertext Links

Navigation through an electronic submission is greatly enhanced by the appropriate use of bookmarks and hypertext links. ICH Q&A number 53 states, "It is expected that any document that has a Table of Contents (TOC) will have bookmarks (see the eCTD specification for details). Documents without TOCs should have bookmarks included where it aids in the navigation around the document content. For example, a 4 pages long document that is summarising findings could require bookmarks to aid navigation. However, a 300 pages long file containing a single data listing might not require bookmarks as there is no further internal structure. Please consult regional guidance documents for further details."

In general terms, bookmarks and hyperlinks should be used to aid navigation. The overuse of hyperlinks may confuse rather than help assessors and may cause problems later in lifecycle management. However, hyperlinks back to previously submitted documents are welcome if pointing to the correct location.

Additional details on creating bookmarks and hypertext links in PDF documents can be found in the ICH eCTD specification, Appendix 7.

With the current version of the eCTD specification, it is not possible to cross refer from one eCTD application to another.

2.9.8 Node Extensions

Node extensions may be used where additional navigation in the XML backbone is required. The primary place where they are used is in Module 5 where a node extension for each study is useful to group together the multiple leaves that make up the study and its modular appendices, in a study specific folder. Also, it could be useful to differentiate reports associated with a different dosing regimen for the same indication. For Module 4 when submitting reports consisting of multiple pdf files, node extensions can also be useful with an associated subfolder. In Module 1, node extensions should be included to differentiate the responses at different stages of the lifecycle. For further details on responses, see section 3.2.6. Currently, additional folders in m1-responses are not allowed and therefore, the use of an additional folder in combination with a node extension is not possible.

Please note, the use of node extensions should be limited to those areas where it is critical, and consideration should be given regarding the impact of the view for the reviewer since the inconsistent use of node extensions can lead to unanticipated effects in the cumulative view of a submission.

When node-extensions are used the 'title' attribute in the XML backbone must have a value.

2.9.9 Extensible Mark-up Language (XML)

XML is the format for the backbone files for the eCTD. Details on XML can be found in the ICH eCTD specification, Appendix 7.

2.9.10 Working documents

Other file formats such as MS Word formats may be required by EDA *in addition* to the PDF requirement of the eCTD, especially for the provision of product information documents or the Module 2 documents. The files referred to above should not be added as leaf elements within the eCTD structure. When submitted with an eCTD, they should always be provided in a separate folder called "xxxx-workingdocuments" on the same submission zip package containing the eCTD, where the number (xxxx) matches the number of the eCTD sequence being submitted.

Important note: for EG submissions validation reports **must NOT be included** in the working documents folder. These are not required and including them causes additional work for EDA staff.

2.9.11 Technical Validation of eCTD Submissions

The technical validation of an eCTD is a separate activity compared to the content validation of a submission and takes place irrespective of the type of the submission. EDA has adopted a common set of technical validation criteria against which all eCTDs can be checked using eCTD review and validation tools. It is strongly recommended that all sequences are checked and found technically valid according to the published validation criteria.

Two categories of validation rules apply: "Pass/Fail", and "Best Practice":

Pass/Fail Criteria

This is a set of technical validation criteria that can either be passed or failed. eCTDs that fail to meet one or more of these criteria will be rejected and a resubmission of the same sequence number will be required. All eCTD submissions via the EDA Portal to EDA are automatically run through a full technical eCTD validation and an automated 'success' or 'failure' acknowledgement is sent to the applicant/MAH by email.

Best Practice Criteria

These are validation criteria that are considered good practice to facilitate the review of an eCTD.

The applicant should make every effort to address these areas before the eCTD is submitted. eCTDs that fail to meet one or more of these criteria will still be accepted by the authority during technical validation and it is possible that the authority may not even check these criteria during technical validation.

Note: These criteria cannot test the correctness of the metadata. Therefore, applicants need to make sure that all metadata are filled in correctly.

Please do not add any documentation, including validation reports directly into the submission folder as this will cause a technical validation failure.

Errors found during the content validation, e.g. mistakes in an application form to be corrected, should be resolved through the submission of a new eCTD sequence using the next sequence number. These errors, which are content errors, must never be resolved by resubmitting an existing sequence by re-using the same sequence number.

2.10 Other Technical Information

2.10.1 Protection against Malware

The applicant is responsible for checking the submission for malware such as viruses. Checking should be performed with an up-to-date virus checker. After receipt at EDA, a similar internal virus check will be performed. If a virus is detected it will constitute grounds for technical invalidation of the submission.

2.10.2 Security Settings

Submission or file level security is not permitted. If one-time security settings or password protection of electronic submissions are used this could constitute grounds for the rejection of the submission.

There must be no security setting to open any individual file. This includes passwords, certificate security, adobe policy server settings, etc.

Furthermore, there must be no security settings applied to any individual file, this means that security settings in for example Adobe Acrobat, all "restrictions" should normally be "allowed" when viewing the Document Preferences > Security settings. If for some reasons this is not possible for some documents, e.g. for digitally signed documents, as a minimum printing and content copying need to be allowed.

2.10.3 Signatures

Electronic signatures are not used for documents used in eCTD submissions to EDA.

2.11 Technical Baseline Applications

A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to the EDA but in another format. The sections provided to make up a baseline are be defined by the authority, but

any omissions should not render the submitted content misleading. Please refer to the baseline guidance document published on the EDA website.

It is required to use a baseline as a start of an eCTD when changing from paper or Non eCTD Submission and to provide as much content as possible in the eCTD. The baseline would preferably consist of high-quality electronic source documents, but good quality scanned images would also be acceptable in these cases, preferably with Optical Character Recognition (OCR) to facilitate text searching.

It should be clearly stated in the cover letter of the "baseline eCTD sequence" that the content of the previously submitted dossier has not been changed, only the format. There is no need for the EDA to assess baseline submissions and hyperlinks between documents are therefore not needed. The submission type *reformat* should be used in the envelope for the baseline sequence.

2.11.1 Baselines Starting as Sequence 0000

The baseline should normally be submitted as sequence 0000, always be a separate submission and should never include new applications. The first new regulatory activity, e.g. the next variation, in eCTD format should then be submitted as sequence 0001, see table below.

Table 3: Example for starting an eCTD with a baseline sequence

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0000	Baseline	None	0000	reformat
0001	Variation for new indication of COPD	var-pac-II	0001	initial
0002	Response to Questions	var-pac-II	0001	response
0003	Variation to shelf life	var-pac-b	0003	initial

2.11.2 Re-Baselining a Broken eCTD Lifecycle

One of the principles of eCTD is that with the use of the operation attributes, it is possible to manage the lifecycle of a product and generate a view of the "current dossier".

However, in certain cases, the lifecycle at the side of the applicant may be broken. This situation can occur in cases such as:

- An MA is transferred to another MAH who is unable to import any existing eCTD sequences into its building tool.
- An applicant switches to a new publishing tool and is unable to import their submitted sequences.
- An applicant is working with a lifecycle where previously submitted sequences are actually technically invalid, but were not technically validated at the time by the receiving agency.

The problem with all of these situations is that the applicant cannot continue with the existing lifecycle of the product. Any subsequent submission (sequence) for the product where previously submitted content is changed and needs to be referred to (using the operation attributes replace, or delete) cannot be built in the tool, or, if built, would be invalid. This is because it is impossible to create the link back to the original submitted documentation, because it no longer resides in the eCTD building tool.

In these first three examples, the preferred situation would be that the previously submitted sequences are imported in the new tool, and the lifecycle of the product will continue. However, this might not be possible, due to technical issues in uploading previous sequences into a different tool, or particularly when the previous sequences were invalid. If the lifecycle re-starts a new UUID for the application is required.

In addition, in exceptional cases, there may be a benefit to both the applicant and to the agency if the current lifecycle is archived in some way and re-started.

For example: An applicant has submitted in the past an eCTD application under current guidelines, and there is a change in general regulatory guidelines that affects the whole dossier content.

To ensure that the lifecycle of the product is correctly maintained going forward, it is proposed that in these exceptional circumstances, and with prior agreement between the MA holder and EDA, applicants are allowed to resubmit the current registered dossier as a baseline consisting of all valid documents as seen in "current view", leaving the existing sequences in place, but essentially resubmitting the content in a new eCTD application. Also, in these cases a new UUID for the application is required. It is strongly recommended to finalize ongoing regulatory activities before submitting the baseline.

In the cover letter the applicant must provide details of why the lifecycle is broken and state that a baseline eCTD sequence is being submitted in order to restart the lifecycle.

- A new UUID needs to be assigned to the application.
- The submission type would be "none"
- The submission unit type would be "reformat".
- The operation attributes of the leaves would be all "new".
- The sequence number of the submission would normally be restarted at 0000 and not continued from the previous lifecycle, since continuation of existing numbering could lead to complex lifecycle issues.

Re-baselining where the previously submitted sequences cannot be used in the new lifecycle and must be archived

For the authority, the former submitted sequences have to be handled as "history", and the new set of sequences would need another identifier to be set by the authority to differentiate them from this previous lifecycle. The lifecycle will begin from scratch again from the time of the baseline submission with a new UUID. There is no need to mention the previous (archived) sequences in the tracking table, so the new tracking table should only refer to the re-established lifecycle.

Scenario 1 – Scenario on Re-baselining a Broken eCTD Lifecycle
Applicant X has submitted sequences:
0000 Initial application
0001 Validation update
0002 Response 1
0003 Response 2
0004 Variation 001
** Problem occurs in continuing lifecycle, **see examples below**
0005 ⟹ 0000 - Next submission

0005 is not submitted. Instead, 0000 - 0004 are archived, and a new eCTD is started at 0000.

Examples for this scenario:
** MA is transferred, previous sequences 0000-0004 cannot be imported into a tool by the new holder.
** Applicant changes their eCTD Building tool, previous sequences will not import into the new tool

2.12 Procedure for Sending Electronic Information

All submission must be submitted via the EDA online portal located at https://reg-submit.edaegypt.gov.eg.

All users of the portal must be pre-registered.

When using the portal, applications can be created for various regulatory activities and an eCTD sequence in a zip format and can be uploaded for processing by EDA, please refer to the 'Applicant Portal Guide' for further information on accessing and creating a submission.

3 Module Specific Information

3.1 General Information

The following subfolders should be used to organise the files for each module in a submission: *m1, m2, m3, m4,* and *m5* following the principles set out for the CTD according to EG eCTD m1 Specification and ICH eCTD specification 3.2.2.
There is also a subfolder *util* to organise eCTD technical files in the submission. If a module is not appropriate for a particular submission it should be omitted. Empty subfolders should not be included.

Each document should be provided as an individual PDF file, except those specifically requested in a different format.

3.2 Module 1 eCTD Envelope, Administrative Information and Prescribing Information Folder

3.2.1 General Considerations

"Not Applicable" Module 1 documents should not be included in eCTD. However, when a justification for the absence of a certain document in Module 1 is required, such justification should be provided in its corresponding section in the eCTD structure. In any case, all section titles should always appear in the Module 1 eCTD backbone, displayed by the style sheet, even if these sections are not populated.

3.2.2 Creation and Management of Envelope Information

The eCTD envelope should be used to describe the eCTD sequence:

Identifier A UUID as specified by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834- 8:2005. The same UUID will be used for all sequences of an eCTD application.

Submission Type	This value represents the regulatory activity which will be started and the type of material sent to the agency. The entry is chosen from a Controlled Vocabulary provided on EDA's webpage.
Submission Unit	Submission unit type describes the content at a lower level (a "sub-activity") which is submitted in relation to a defined regulatory activity. The entry is chosen from a controlled vocabulary on EDA's webpage.
Submission Mode	This element should only contain a value in case of variations regulatory activities and must be included in every sequence of that activity. The entry is chosen from a controlled vocabulary on EDA's webpage.
Submission Number	This number represents the High-Level Number. The high-level procedure number related to the regulatory activity in case of submissions of grouped variations if **multiple** products are concerned**.** Samples are provided in the EG M1 Specification. Note: not required in case only one product is concerned. If submission mode is set to 'grouping' there should be a Submission Number (Number element in the DTD). This Number element should be identical with the variation procedure number included in a Variation Application Form.
Procedure Tracking Number	Always to be completed. Any value used by the authority or applicant to track the submission, in any procedure, in relation to a particular product. In case of using the submission number, the Procedure Tracking Number (PTN) refers to the product involved in the grouped submission.
Applicant	Entries for 'applicant' should be consistent for all eCTDs from any single applicant (legal entity), as they define where eCTDs are stored in internal systems. Consistency of spelling is also relevant over time to allocate the eCTD correctly.
Authority Code	This authority code is 'EDA' for Egypt.
Invented name	The trade name/invented name for the medicinal product covered by the application. This entry does not need to describe the complete name, a simple entry, for example, 'Wonderdrug' will suffice.
INN	The International Non-Proprietary name for the drug substance.

Sequence	The sequence number here must match the sequence number in the folder structure and on the Cover letter.
Related sequence	For a description and example of how to use the 'related sequence' entry, see Section 2.9.5 and the EG M1 Specification.

Submission-description This element is used to describe this particular eCTD sequence.

Registration Type	Provides information associated with the registration of the product**,** e.g. Imported Finished or Imported Bulk. The list is available in the Registration Type Controlled Vocabulary published on the EDA web site.
Marketing Type	Provides information associated with the marketing of the product in Egypt. e.g. Local or Tender and Export. The list is available in Marketing Type Controlled Vocabulary published on the EDA web site.

3.2.3 Module 1.0 Containing Cover Letter and Tracking Table

3.2.3.1 Cover Letter

The cover letter should always be submitted with the document operation attribute "new". As eCTD viewing tools will display all "new" leaf elements in a current or cumulative view, it is recommended that additional descriptive text is included in the leaf title to help identify specific cover letters. This will help identify each cover letter leaf and the submission it is in, rather than having the cover letters named the same in each sequence. Some examples for the leaf titles could be:

Cover Letter for Sequence 0000
Cover Letter for Variation 028 (0042)

Please note, when resubmitting content due to technical validation issues or sequences missing at EDA side, a note (a comment in the working documents) may be provided to clarify the reason for resubmitting and the original cover letter in the eCTD should not be changed, see Section 2.9.4. For submissions to the EDA it is mandatory to use the portal.

3.2.3.2 Tracking Table

A tracking table should always be included as an annex to the cover letter. The file should be named tracking-var.pdf and be placed in /XXXX/m1/eg/10-cover/.

An example of a Tracking table that would be suitable for an EDA submission can be found in Annex 2 below.

3.2.4 Forms

3.2.4.1 Application Form

The application form should always be submitted with the document operation attribute "new" (as for the cover letter, see above), unless an error has been made in the form and an updated application form is being provided in a new sequence, in which case the operation attribute should be "replace".

The file named form-af.pdf (without using any variable part of the file name) should be used if only one AF is provided. However, if more than one AF is included in the m1.2, they should be differentiated by the use of the variable part (e.g. form-af-10mg and form-af-20mg).

Additional requested documents for different submission types, which are not part of any M2-5 section or Response to Questions, should be placed in the application form section 1.2. of the eCTD as separate files.

3.2.5 Product information

Product information should be supplied as PDF files within the eCTD. In addition, MS Word files (with or without tracked changes as relevant) should be provided in the separate folder XXXX-workingdocuments (see section 2.9.10) within the same submission.

3.2.6 Use of Response Documents Section

The submission of electronic information in response to a list of questions from EDA should follow the same basic principles as the first submission. The written response should be submitted following the EG recommended response folder and file structure. Please ensure that all documents are aligned with the CTD structure (refer to EG eCTD M1 Specification) using the operation attributes of "new", "replace", or "delete" as appropriate. ("Append" should be avoided, see section 2.9.6.)

To help in the management of responses over the lifecycle of the eCTD, the responses relating to a particular regulatory activity should be grouped under a node-extension in the eg-regional.xml file. The title of the node- extension should identify the regulatory activity (e.g. Responses to Questions for the Initial Application, Responses to Questions for Variation 028, etc.). It is recommended that the applicant provides a full copy of the list of questions received from the authority as the first leaf in this section.

It is recommended that the responses be split up into separate files for each major section of the submission (e.g. Quality, Non-clinical and Clinical). Leaf titles should be used to identify the particular set of responses (e.g. Response to Major Objections - Quality). If responses to more than one question are submitted in a single file, bookmarks should be used within the PDF file to clearly identify each response. It is possible to submit the response to each question in a separate file but in that case node-extensions must be used and leaf titles to group and identify the responses under the top-level node-extension.

In m1-responses, it is recommended to use the variable component of the filename and the leaf title, to present the information clearly to the assessor. The response files should preferably be named as:

responses-<regulatory activity type identifier>-<response number>-<content identifier>.pdf, using the -var component of the filename to define the content.

Table 4: Examples of Filenames and Leaf Titles for Response Documents

Suggested Filename	Suggested Leaf Title
responses-maa-clin.pdf	Clinical Responses, MAA
responses-maa-2nd-clin.pdf	2nd Clinical Responses, MAA
responses-maa-3rd-clin.pdf	3rd Clinical Responses, MAA
responses-maa-3rd-clinq4.pdf	3rd Clinical Response Question 4, MAA
responses-maa-3rd-clinq7.pdf	3rd Clinical Response Question 7, MAA
responses-var03-clin.pdf	Clinical Responses, Var03
responses-var03-2nd-clin.pdf	2nd Clinical Responses, Var03
responses-maa-qual.pdf	Quality Responses, MAA

3.2.7 Use of the Additional Data Section

The section 'Additional Data' should only be used for required information that is not currently included in the published EG eCTD M1 Specification.

In addition, this section can be used for all procedures when an old version of a DTD is being used during an agreed transition period, to support inclusion of a newly defined section of EG eCTD M1 Specification. (refer to transition guidance when issued with specification updates).

3.3 Module 2 Overviews and Summaries Folder

3.3.1 General Considerations

Each document should be provided as an individual PDF.

3.3.2 Structure of Module 2 Documents

In module 2.3 Quality Overall Summary (QOS) either one file (qos-var.pdf) or separate files per QOS section can be submitted named as: introduction-var.pdf, drug-substance-var.pdf, drug-product-var.pdf, appendices- var.pdf and regional-information-var.pdf. For details refer to the 'File-Folder Structure & Names' tab in the EG Validation criteria spread sheet.

Where the application includes an active substance covered by an Active Substance Master File (ASMF), the Applicant should submit the Quality Overall Summary QOS on the applicant's part of the ASMF as a separate file in module 2.3 of the MAA. If there is more than one ASMF, there should be a separate file for each QOS. The Applicant should ensure that each QOS has a front page clearly stating the version number and date.

If an existing document is revised, the lifecycle operator 'replace' should be used. However, if changes of content only affect one section of that document, then updates should normally be submitted as a separate summary with the document operation attribute "new" as it would help clarifying what to assess within the specific submission.

For submissions covering multiple indications, refer to section 3.6.1.

3.4 Module 3 Quality Folder

3.4.1 Module 32S drug substance

This section will give guidance on how to structure the documentation related to the drug substance. Also, please find an example in Annex 3.

In relation to the active substance manufacturer's documentation, the documentation can be part of the complete dossier, be presented as an Active Substance Master File (ASMF) or be covered by a Certificate of Suitability (CEP). The Applicant should provide the documentation on the active substance as relevant in these different situations.

For Biologicals, where the whole active substance documentation would be presented as part of the complete dossier, it is recommended that only one drug substance module (m32s section) should be created even if several active substance manufacturers are used. If there are several different active substances in one finished product (combination product), the documentation should be presented as one drug substance module (m32s section) per active substance.

For all chemical products and products covered by an ASMF, please see the following sections for different scenarios.

3.4.1.1 Active Substance documentation for chemical products and products covered by an ASMF

For the documentation on the active substance for chemical products and products covered by an ASMF, it is important to differentiate between:

- The Active Substance manufacturer´s documentation on the active substance
- The Applicant's documentation on the control of the active substance

The active substance manufacturer's documentation covers how the active substance is manufactured and controlled by the active substance manufacturer to ensure the quality of the active substance (see 3.4.1.1.1).

The Applicant's documentation covers how the active substance is controlled by the finished product manufacturer(s) to ensure the quality of the active substance (see 3.4.1.1.2). This would only be applicable when the active substance and the finished product are manufactured at different sites.

Both the active substance manufacturer's documentation and the Applicant's documentation on the active substance should be provided in the eCTD dossier, as relevant.

Where the application includes an Active Substance covered by an Active Substance Master File (ASMF), the Applicant should submit the applicant's part of the ASMF in module 3.2.S. The Applicant should ensure that the front page of the applicant's part, clearly stating the version number and date, is also included in the product eCTD dossier either as the first page of the first document (i.e. in the nomenclature document) or as a separate file placed in Module 3.2.S.1.1, called *nomenclature-cover page applicant's part.pdf*.

3.4.1.1.1 Active Substance manufacturer's documentation on the active substance

The documentation can be part of the complete dossier, be presented as an Active Substance Master File (ASMF) or be covered by a Certificate of Suitability (CEP). The Applicant should accordingly provide the complete documentation on the active substance, the applicant's part of the ASMF or the CEP, as relevant.

a) <u>If more than one active substance manufacturer for the same active substance</u>

When the active substance manufacturer's documentation is presented as an Active Substance Master File (ASMF), one drug substance module (m32s section) should be created per ASMF i.e. each applicant's part should be presented in its own drug substance module.

When the active substance manufacturer's documentation is part of the complete dossier (i.e. not provided as an ASMF), one drug substance module (m32s section) can be created per active substance manufacturer or one drug substance module (m32s section) can be created covering all active substance manufacturers, depending on whether the documentation is largely similar or not (and same route of synthesis applies).

When the active substance is covered by a CEP, each CEP should be placed in module 3.2. Regional Information If needed, a separate m32s should be created for each active substance manufacturer, where relevant sections of 3.2.S.1 to 3.2.S.7 folders should be used for any additional documents (e.g., for information not covered by the CEP).

b) <u>If multiple active substances in one finished product</u>

Where there are multiple active substances in one finished product (combination product), one drug substance module (m32s section) should be created per active substance and the above guidance for several active substance manufacturers should be followed.

3.4.1.1.2. Applicant's documentation on control of the active substance

The Applicant is responsible for ensuring the quality of the active substance. The applicant should therefore have their own drug substance module (m32s) covering the control of the active substance performed by the finished product manufacturer(s) when the active substance and the finished product are manufactured at different sites.

a) <u>If more than one active substance manufacturer for the same active substance</u>

Applicant's documentation on the active substance should always be compiled; there should only be one drug substance module (m32s) per active substance. It is not acceptable to submit the Applicant's documentation divided into different drug substance modules, even if there are several different active substance manufacturers. It is also not acceptable to provide the Applicant's documentation as separate drug substance modules even if there are several different finished product manufacturers.

b) <u>If multiple active substances in one finished product</u>

Where there are several different active substances in one finished product (combination product), the Applicant's documentation should be presented as one drug substance module (m32s section) per active substance.

If an existing eCTD is not structured in line with the above guidance, the dossier should be restructured with the next submission of a quality variation that affects the relevant content.

See also section 4.4 for information on Active Substance Master Files.

3.4.2 Module 32p drug product

There should only be *one m32p* section even if there are multiple finished product manufacturers. It is *not* acceptable to provide one m32p section per finished product manufacturer for the same dosage form of the finished product. The description of the manufacturing process should be provided as one document within the m32p section (in module 3.2.P.3.3.

If an existing eCTD is not structured in line with the above guidance, the dossier should be restructured with the next submission of a quality variation that affects the relevant content.

3.5 Module 4 Nonclinical Study Reports Folder

3.5.1 Guidance on the Handling of Granular Study Reports

Submissions created in eCTD format for the use within the FDA may provide more granular study reports using study tagging files. There is no need to re-organise the reports for submission to the EDA. See Section 3.6.2. below for further information.

3.6 Module 5 Clinical Study Reports Folder

3.6.1 Management and Handling of Multiple Indications

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section *m535* for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section in *m5* (e.g. m5/53- clin-stud-rep/535-rep-effic-safety-stud/anxiety/5351-stud-rep-contr). If a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate subsection of *m535* and referenced as necessary in the equivalent section under the different indication. In Module 2, a separate "Summary of Clinical Efficacy" module should be submitted for each indication, although closely related indications can be within a single document. Regardless of which way is chosen, it is important to provide clear written guidance to the assessor when the supportive data/study report documents are applicable to more than one indication.

3.6.2 Management and Handling of Granular Clinical Study Reports

ICH Q&A 22 recommends use of E3 granularity for clinical study reports. In Europe, node extensions should be used to group together individual files. If a US NDA is repurposed for submission in the EDA, the study content (the study report and any relevant appendices) should be placed under a node extension. The Study Tagging File (STF) xml file itself and any content not required for the EDA submission (e.g. datasets) should be removed, but submissions still containing STF files will not be rejected. In order to maintain a consistent looking eCTD lifecycle and table of contents (via index.xml), applicants are advised to use node extensions for all clinical study reports, regardless of the granularity of the content (i.e. even reports that consist of only one document should also be presented in node extensions). See also Section 2.9.8 Node-extensions.

3.6.3 Provision of Case Report Forms (CRF) and Data when Requested

If case report forms and individual patient data listings are submitted in m537 (as appendices 16.3 and 16.4 in the ICH clinical study report guideline E3) they should be placed in the same order as the clinical study reports appearing in m535 and should be indexed by study. Please note that bookmarks will not be required as there will be no further internal structure.

3.6.4 Provision of Synopses of Individual Studies

It is acceptable either to include copies of the synopses for each study in eCTD section 2.7.6 or to provide hyperlinks to synopses located in Module 5 without providing copies in section 2.7.6. In either case a Listing of Clinical Studies should be provided, and this should include hyperlinks to the first page of each synopsis.

3.6.5 Company Core Data Sheet

If companies submit their Company Core Data Sheet, this is recommended to be provided in eCTD section 5.3.6, Post Marketing Experience.

4 Advice on Specific Application Types

4.1 New MA Applications

The recommended start for an eCTD lifecycle is the initial MA application. It should normally be provided as sequence 0000. All documents included should have the operation attribute "new" and be placed in the relevant sections in line with the different eCTD specifications.

Refer to Annex 6 for the applicable submission types for new MA applications.

See Section 2.9.5 for an example on the use of the submission units.

For responses to questions documents, see Section 3.2.6.

4.2 Variation Applications

All types of variations should be submitted within the eCTD as new sequences.

Documents related to the variation should be included in relevant sections or be deleted or replaced by use of the appropriate document operation attribute. Where documents cannot be assigned to specific CTD defined locations, then they should be provided as annexes to the m1.2 Application Form.

The submission type should reflect the type of variation.

See Section 2.9.5 for an example on the use of the submission units.

For details on how to handle parallel variations, please refer to Annex 4 of this guidance.

4.3 Renewal Submissions

Please note that a renewal application can be used as the first eCTD in a product lifecycle. The recommendation given in the section above applies likewise.

The submission type should be "renewal".

See Section 2.9.5 on examples on the use of the submission units.

4.4 Active Substance Master Files

For Marketing Authorisation Applications (MAAs) in eCTD format, where the documentation on the active substance is presented as an Active Substance Master File (ASMF), the applicant should incorporate the applicant's part (AP) documents of the ASMF and the Quality Overall Summary (QOS) on the applicant's part of the ASMF into the eCTD structure as per the relevant guidelines. It is recommended to use a suffix of '-ap' on the filename of these documents.

The ASMF Holder should provide the full ASMF, i.e. both the Applicant's and the Restricted part in eCTD format to EDA. The Applicant's part and the Restricted part should each have a front page clearly stating the version number and date.

The ASMF should include a QOS on the Applicant's part and a separate QOS on the Restricted part. Each QOS should have a front page clearly stating the version's number and date.

A copy of the "Letter of Access" addressed to the EDA should be placed in m1.2.

4.5 Plasma Master Files (PMFs) and medicinal products containing PMFs

4.5.1 Plasma Master Files

The Plasma Master File documentation for certification is submitted to the EDA as a stand-alone eCTD dossier of a medicinal product. This documentation contains all the information related to the starting material for the manufacture of the medicinal product but submitted separately from MAA dossier when follows the PMF certification evaluation procedure.

4.5.2 Medicinal products containing PMFs

All concerned medicinal products that include one or more plasma suppliers in their dossier (i.e. one or more PMF(s)) are required to have their dossier updated and implement any updates by submitting the relevant variations to the MA (see point 4.2 above).

4.6 Applicant Initiated Withdrawal of the MA

Applicants may decide to withdraw their marketing authorisation during any stage of the product lifecycle, and this section explains the general principles that should be followed in terms of managing the eCTD lifecycle.

Withdrawal of the product covered by an eCTD should preferably be submitted as a new sequence only including a cover letter with the request for withdrawal. The operation attribute "delete" is not required to be used for the documents.

The submission type 'withdrawal' should be used for this regulatory procedure.

4.7 Applicant Withdrawal or Authority Rejections of Post-Authorisation Regulatory Activities

If a regulatory activity is withdrawn, fully or partially or rejected fully or partially, then the documentation has to be updated accordingly with a consolidation sequence. Documents that are no longer relevant should be deleted, and documents where the content needs to be adjusted to reflect the withdrawal or rejection be replaced. The application form and cover letter should always be retained to keep the history. A consolidation sequence should be submitted to restore the current view of the dossier to what it was before the rejected activity was submitted. The submission unit type should be 'Response'. Note, it is not possible to delete a sequence from the life cycle to accommodate the withdrawal or rejection.

Scenario on consolidation sequence

Applicant X has submitted sequences:

0027 Variation 011
0028 Response Letter of rejection of variation 011
**0029 consolidating sequence to restore the previous status of dossier
0030 Variation 012
0031 = Next submission

The variation 011 has been rejected and those parts affected by the proposed variation need to be restored to present the previous status in the current view of the eCTD.

Examples for this scenario:

** After full or partial rejection of sequence 0027, (variation 011), a following sequence 0031 may change the same technical content. If the change previously applied for in variation 011 has not been fully restored, the new variation may not be displayed correctly, for example, the next submission cannot refer to content which was proposed in variation 011 but subsequently removed. Therefore, the consolidating sequence, 0029, must remove any new and now rejected content from the rejected variation, and also reinstate any documents that were deleted or replaced in sequence 0027/0028, such that sequence 0030 can itself replace or delete the content as required. i.e. Sequence 0029 must restore the current view, (in terms of what is current, not deleted or replaced), to what it was before sequences 0027 and 0028 were submitted.

Annex 1: eCTD Reference Documents

It is recommended to regularly follow the information on the following websites:

The EDA eCTD Webpage with for example the EG Module1 Specification and other eCTD v.3.2.2. EG specific information like guidance documents and the EG Validation Criteria.

ICH Electronic Standards (e.g. eCTD 3.2): https://www.ich.org/page/electronic-standards-estri

There is also other relevant information to be considered:

- http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- https://admin.ich.org/sites/default/files/inline-files/eCTD_v3.2_Q%26A_%26_Specification_Change_Request_Document_v1.33.zip
- https://admin.ich.org/sites/default/files/inline-files/Specification_for_Submission_Formats_for_eCTD_v1_3.pdf

ICH M4, CTD information

- ICH Official web site: ICH

EDA Portal: https://reg-submit.edaegypt.gov.eg/

Annex 2: Tracking Table Example

A2-1 Introduction

A Tracking table is required for all eCTD submissions within all procedure types; this is an example of a Tracking table in a suitable format for submissions.

A2-2 Tracking table example

Product Name/Number

Table 5: Tracking table example

Sequence Number	Submission Description	Submission Date
0009	Variation PAC-II	Oct-2024
0008	CMC VAR PAC IB product - change in the retest period	Sep-2024
0007	Variation PAC-II	Dec-2023
0006	Variation PAC-B	Jul-2023
0005	Response to Specific Obligations	Sep-2022
0004	Letter of Commitment - Responses	Jun-2022
0003	Consolidated Responses	Jun-2022
0002	Responses to List of Outstanding Issues	May-2022
0001	Responses to List of Outstanding Issues	Feb-2022
0000	MAA	May-2022

Annex 3: Guidance and Best Practice on the Structure of Module 3

CTD-Quality Considerations for eCTD Submissions in Egypt

A3-1 Introduction

This Annex is based on the use of the ICH eCTD specification v3.2. Refer to the Glossary for an explanation of terms.

The ICH eCTD Specification allows the applicant to manage eCTDs at different levels in Module 3 (please, refer to section 2.2. above).

A3-1.1 Terminology in the eCTD module 3 XML

In addition to documents, eCTD applications provide information in the XML as follows:

- Attribute: Defines new sections within the CTD table of contents (e.g. substance, manufacturer)
- Element: The CTD table of content location (e.g. m3-2-s-1-1)
- Leaf: eCTD document
- Module 3 attributes examples
    - m3-2-s-drug-substance: *substance, manufacturer*
    - m3-2-p–drug-product: *product-name, dosage form, manufacturer*
    - m3-2-p-4–control-of-excipients: *excipient*

A3-2 General Principles

These XML attributes describe the quality sections of the eCTD and should be chosen carefully to present the information provided to the assessor in a clear and unambiguous way. See sections 3.4.1 and 3.4.2 in relation to the structure of the drug substance and drug product modules.

A3-2.1 Document Granularity

eCTD applications can handle different authoring strategies for CTD-Q information. For any given CTD-Q topic (e.g., P.1 Description and Composition of the Drug Product), either a single document can be provided that covers multiple strengths, or multiple documents can be provided, e.g. per strength. Regardless of the XML attributes, when there are significant differences in content it is best practice to provide multiple documents, to realise the lifecycle benefit that eCTD offers. When deciding on the strategy for the single- or multiple-document approach applicants should also take into consideration the ability of the assessor to review the content. If there are multiple files in the same element, the title of each leaf should be used to distinguish the scope of each document's content, and the –var part of the filename used to differentiate each PDF document.

A3-2.2 Identifying to EDA what the Application covers

Generally speaking, a single eCTD application is submitted for each strength and forms under one tradename. In Egypt, the applicant cannot cross-refer from one eCTD to another (e.g., for drug substance).

A3-2.2.3 EG Envelope

The Module 1 EG envelope provides the trade name (invented name) of the drug product. The **procedure tracking number element,** which is repeatable, may list all of the product licences or application numbers covered by the eCTD. Applicants should ensure that the values for invented name, INN Applicant and Application Number in the EG envelope are complete and consistent.

Note: The Application Number and INN may not be known at the time of the first submission and may have to be substituted in later sequences.

A3-3 Module 3 XML Attributes in the eCTD

A3-3.1 Choosing Module 3 XML Attributes

The XML attributes reflect the document granularity used in Module 3. The actual words for the attributes need not be an exact match of the words used in the content of Module 3 documents but should clearly describe the content in that specific section of the dossier. More than one entry for any attribute generally results in the replication of the relevant portion of both the XML and the folder architecture, (e.g., 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.P.4 Control of Excipients, 3.2.A.1 Facilities and Equipment, 3.2.A.2 Adventitious Agents Safety Evaluation, 3.2.A.3 Excipients).

Module 3 XML attributes cannot be changed with later submissions within the same application without losing the lifecycle benefit that eCTD offers. For example, if an applicant builds an eCTD with “ABC Chemical” as the manufacturer of the drug substance, and subsequently changes drug substance manufacturer to “XYZ Chemical”, they would normally provide a new eCTD sequence with “XYZ Chemical” as an additional module 3 XML attribute. It will not be possible to have content in the “XYZ Chemical” section that replaces or appends to content in the “ABC Chemical” section. This is because in the eCTD it is not possible to apply lifecycle across different sections. However, it will be possible to delete some or all of the content within the “ABC Chemical” section, if required.

A3-3.2 Drug Substance(32s) Attributes

The use of these attributes is mandatory. Refer to ICH eCTD Q&As #65-70 for guidance. (Change control section at bottom of page).

A3-3.2.1 Example – One Drug Substance, two Drug Substance Manufacturers, two Finished Product Manufacturers, one Dosage Form

In this example, there are two drug substance manufacturers, which each hold an ASMF on the drug substance. The MAH/Applicant should create three drug substance modules in their eCTD dossier:

- The Applicant's part of ASMF 1 in one drug substance module (m32S section).
- The Applicant's part of ASMF 2 in one drug substance module (m32S section).
- The Applicant's control of the active substance in one drug substance module (m32S section), which covers both sources of the drug substance.

The drug product module should be compiled covering both finished product manufacturers i.e. there should only be one drug product module:

- Drug product (m32P section)

Table 6: Example Drug product (m32P section)

Drug substance:	INN
Finished product:	INVENTED NAME 400 mg film-coated tablets
Drug substance manufacturers:	Y (ASMF holder 1) X (ASMF holder 2)
Finished product manufacturer:	Z and A

- m3-quality
  - m3-2-body-of-data
    - m3-2-s-drug-substance [manufacturer: X] [substance: INN]
    - m3-2-s-drug-substance [manufacturer: Y] [substance: INN]
    - m3-2-s-drug-substance [manufacturer: Applicant] [substance: INN]
    - m3-2-p-drug-product [manufacturer: All] [product name: INN] [dosage form: 400-mg-FCT]

The manufacturer of the drug product is stated as "all" as the documentation is compiled and covers all drug product manufacturers of this specific dosage form. '

A3-3.3 Drug Product (32p) – Product/Dosage Form/Manufacturer

The use of these attributes is optional. Refer to ICH eCTD Q&As #68, 69 and 70 for guidance.

A3-3.3.1 Drug Product Name

Since the M1 EG envelope contains the invented name, it is not necessary to use this name in the product name XML attribute that is used in Module 3. Applicants should take into consideration that trade names can occasionally change over time. If the trade name is not well established, applicants should consider alternatives such as 'active', or 'product'. Alternatively, the internal company code of the drug product name may be used. If applicable, additional attributes can be used as needed (e.g. 'diluent' or 'placebo').

This attribute then results in a full set of 3.2.P.1 to 3.2.P.8 XML elements and folders.

A3-3.3.2 Drug Product Manufacturer

Normally, there should only be one drug product manufacturer section in an eCTD dossier. A general term for the attribute such as 'all' or 'applicant' is acceptable.

However, for some product types, e.g. biotechnological products, there might be relevant to have multiple drug product manufacturer sections. If used and in conjunction with the above product name and dosage form, each manufacturer entry results in a set of 3.2.P.1 to 3.2.P.8, 3.2.A.1 or 3.2.A.2 XML elements with appropriate directory folders.

A3-3.4 Excipients

The use of these attributes is optional. Detailed guidance is provided in the ICH eCTD IWG Question and Answer and Specification Change Request Document, Q&A #72-75 (link in previous section)

A3-3.4.1 Excipients of Human or Animal Origin and Novel Excipients

Content under sections 3.2.P.4.5 & 3.2.P.4.6 should be provided under an additional attribute such as 'animal-human-novel', refer to ICH eCTD Q&A #73. Note, the files provided under this section should not be in a subfolder to the 32p4-contr-excip folder in the directory structure. Refer to the 'File and Folder Structure Names' worksheet in the eCTD validation rules.

Annex 4 Management of Parallel Variations in the eCTD

A4-1 Background

Parallel variations are variations on-going within a single product lifecycle at the same point in time that are modifying the same content. Tracking these variations and modification of the content representing the current-approved baseline represents a particular business challenge within eCTD.

This annex presents the recommended approach for managing parallel variations in accordance with the ICH and EG eCTD Specifications.

A4-2 Business Challenge

Parallel variations occur when more than one variation is submitted modifying the same approved content, the first of which has not been approved before the next is submitted. Upon approval of one of the variations, the approved content has changed. The remaining pending variations contain proposed content that may be based upon the originally approved content or on the newly approved content. The applicant must track each separate approval and update the content for each pending variation.

The specific challenges associated with this sequence of events are as follows:

(i) Tracking the approved content
(ii) Tracking separate on-going variations
(iii) Tracking individual or combined approvals for each variation

A4-3 Best Practice

Two options are described

- Option 1 is the classic approach to eCTD lifecycle management, where a single document is replaced by a different, updated version, at the initial submission.

- Option 2 involves leaving the ‘approved’ content in the eCTD, but introducing ‘proposed’ documents into the lifecycle, until the outcome of the assessment is clear, and only then replacing the original ‘approved’ content.

This best practice can provide no guidance on when to use the technique described in option 2, and when to assume that a variation is not happening in parallel, and therefore to use option 1, submitting the proposed content as a leaf with the ‘replace’ operation attribute. Applicants need to consider whether or not it would be appropriate to use the one or the other option outlined in this guidance on a case-by-case basis.

A4-4 Description of Figures

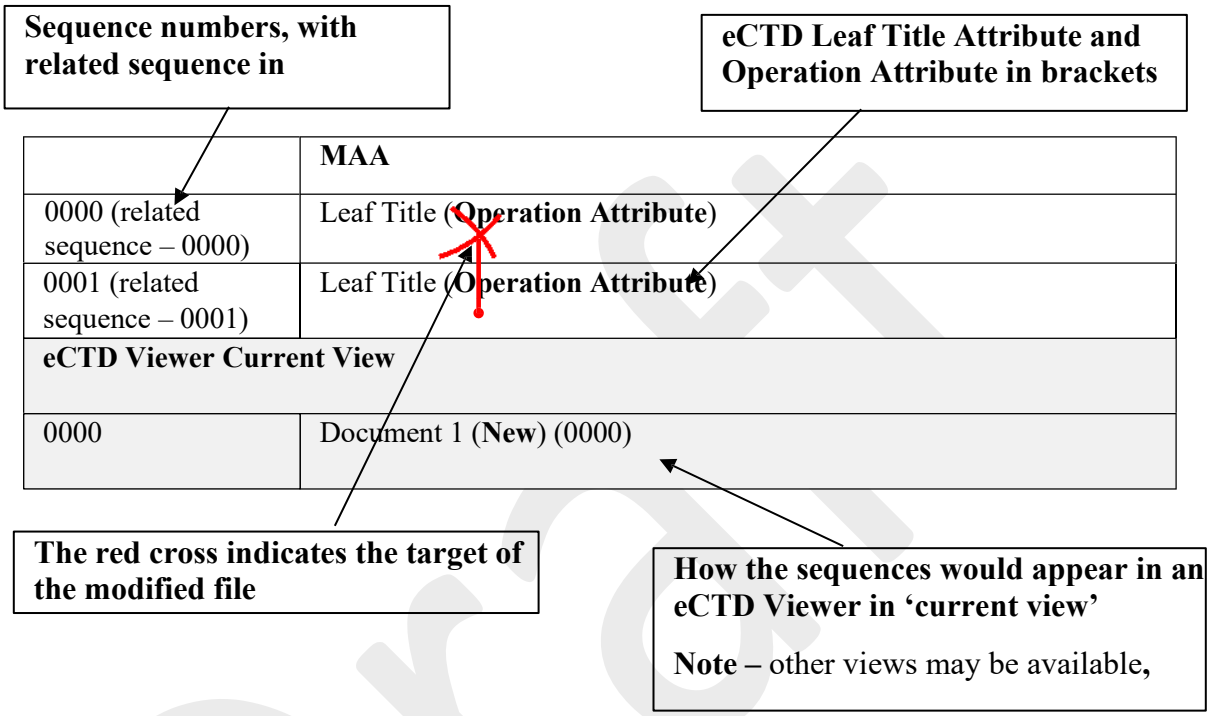


Figure 1 (A4): Description of elements

A4-4.1 Use of one Lifecycle (Option 1)

This option describes the classic eCTD lifecycle management approach, where existing content is replaced with revised content. When there is only one change and variations do not occur in parallel, and the change is approved, the advantage of this approach is that applicants do not have to follow up with another consolidation sequence after approval, because they have already replaced the content, and the current view of the eCTD will be correct.

Figure 2 (A4): Use of one document lifecycle

	MAA & Variations
0000 **(**MAA**)** (related sequence – 0000)	Document 1 **(New)**
0001 (Variation 1) (related sequence – 0001)	Document 1 Proposal 1 **(replace)**
0002 (Variation 2) (related sequence – 0002)	Document 1 Proposal 2 **(replace)**
	eCTD Viewer Current View
0000	Document 1 **(New)** (0000)
0000 - 0001	Document 1 Proposal 1 **(replace)** (0001)
0000 - 0002	Document 1 Proposal 2 **(replace)** (0002)

A4-4.1.1 Drawbacks of Option 1

Approval Status and Clarity on the Basis for Further Changes

If option 1 is used, and the most recently submitted document is replaced, regardless of its regulatory status, then it becomes unclear what has been approved, and therefore what the changes in the incoming new submission are based upon. In this example, it is unclear whether Proposal 2 is based on the content from Proposal 1 or the content from the original Document 1 in sequence 0000. Therefore, when using this approach, if a second variation is submitted before the first is finalised, applicants should specify which document the changes in the second variation are based on.

Impact of Regulatory Outcome

If the operation attributes ‘replace’ is used in each variation as described in Figure 2, then depending on the progress of the review/approval/rejection of each variation, the eCTD lifecycle may not correctly represent the current or most appropriate lifecycle. For example, if variation 2 were to be approved first, the documentation of variation 1 where changes were based on the content in sequence 0001 may no longer be displayed appropriately. If variation 1 is rejected, and variation 2 was based on changes versus the content in variation 1, the content of variation 2 might be difficult to evaluate.

If either variation 1 or 2 (or both) is rejected, a new sequence has to be submitted reflecting only the approved content. One advantage of this approach is that if both variations are approved, no additional sequence has to be submitted.

A4-4.2 Creation of separate Approved and Proposed Document Lifecycles (Option 2)

This option can be used in any situation where parallel variations are expected, but this is specifically recommended when submitting labelling changes of an application, and the terminology used here is therefore specific to the SmPC in applications. When an applicant expects parallel variations to be submitted, the proposed document for the variation is not submitted as a replacement of the original (approved) content. Instead of using operation attribute "replace", a new document lifecycle is created for each proposed document by submitting it with a title identifying its proposed status and a very brief description of the change being proposed, and an operation attribute of "new". Proposed content submitted in this way can only be submitted as a "new" document or replace other proposed content in the same location. The approved content in this CTD section has a separate lifecycle and has a title indicating it is the approved document. This means that eCTD viewing tools will allow viewing of both the approved and proposed content alongside each other in the eCTD "current" view. Specifically, for the m1.3.1 section of the dossier 'approved' documents should be labelled with e.g. "Approved Version"' in the leaf title. Variations are then submitted as 'new' documents, not replacing this approved content, with appropriately descriptive leaf titles, for example, "Variation Section 4.4 Update June 2025 - Proposed".

A4-4.2.1 Addition of further proposed Document Lifecycles (parallel variations)

If, during the review of the first variation, there is a subsequent variation that also proposes changes to the same content, this is also submitted with an operation attribute of "new", and a title indicating that the document being provided is another proposal. The document submitted in the second proposal should reflect changes made versus the current approved document (in this example, the current decision); the document does not contain the changes from Variation 1. The leaf title should differentiate it from the former proposed document from the previous variation. Assigning descriptive title attributes will allow the proposed document in each variation to be identified by viewing tools displaying the "current" view.

Figure 2 illustrates how the "current" view is able to display each of two parallel variations, when the title attribute is specific to the variation and the operation attribute "new" is used as described.

Figure 3 (A4): Use of separate document lifecycles with different title attributes

	Original MAA	**Approval**	**Variation 1**	**Variation 2**
0000 (rel sequence – 0000)	Proposed SmPC (**New**)			
0001 (rel sequence – 0000)	Changes to SmPC 1 **(Replace)**			
0002 (rel sequence – 0000)	Changes to SmPC 2 **(Replace)**			
0003 (rel sequence – 0000)		SmPC Decision July 2025 **(Replace)**		
0004 (rel sequence – 0004)			Variation Section 4.4 Update July 2025 - Proposed (**New**)	
0005 (rel sequence – 0005)				Variation Section 4.6 Update August 2025 - Proposed (**New**)
	eCTD Viewer Current View			
0000	Proposed SmPC (**New**) (0000)			
0000 - 0001	Changes to SmPC 1 (**Replace**) (0001)			
0000 - 0002	Changes to SmPC 2 **(Replace)** (0002)			
0000 - 0003	SmPC Approval July 2025 **(Replace)** (0003)			
0000 - 0004	SmPC Approval July 2025 **(Replace)** (0003) Variation Section 4.4 Update July 2025 – Proposed **(New)** (0004)			
0000-0005	SmPC Approval July 2025 **(Replace)** (0003) Variation Section 4.4 Update July 2025 – Proposed **(New)** (0004) Variation Section 4.6 Update August 2025 - Proposed **(New)** (0005)			

A4-4.2.2 Upon Approval of a Single Variation – Deletion and Replacement

Upon approval of any variation, the proposed content is deleted, and the original (approved) content is replaced with a document containing the revised content. Current view will then show the newly approved content, but also any outstanding proposals, as shown in 3 and Figure 4. This additional sequence should be considered part of the same regulatory activity as the proposal that has been approved.

Figure 4 (A4): Replacement of approved content by newly approved content, and deletion of proposed content

In this example, EDA decision received in December 2025 incorporates the changes from the Variation submitted in sequence 0004 only. The changes from the Variation in sequence 0005 are still under review. In sequence 0006, the 'proposed' label from the first variation is deleted and the new EDA decision is provided, replacing the original commission decision from sequence 0003. The content of the second variation is also amended in sequence 0006, to reflect the newly approved content in section 4.4, alongside the still unapproved change in section 4.6, and left in the lifecycle as an outstanding proposal.

	MAA	**Approval**	**Variation 1**	**Variation 2**
0003 (rel sequence – 0000)		SmPC (English) Decision July 2025 **(Replace)**		
0004 (rel sequence – 0004)			Variation Section 4.4 Update July 2025 - Proposed (**New**)	
0005 (related sequence – 0005)				Variation Section 4.6 Update August 2026 - Proposed (**New**)
0006 (rel sequence – 0004, 0005)		SmPC (English) Decision Dec 2025 **(Replace)**	Variation Section 4.4 Update July 2025 - Proposed (**Delete**)	Variation Section 4.6 + inclusion of approved Variation Section 4.4 Update Dec 2025 – Proposed (**Replace**)
	eCTD Viewer Current View			
0000 - 0005	SmPC (English) Decision July 2025 (**Replace**) (0003) Variation Section 4.4 Update July 2025 - Proposed (**New**) (0004) Variation Section 4.6 Update August 2025 - Proposed (**New**) (0005)			
0000 - 0006	SmPC (English) Decision Dec 2025 **(Replace)** (0006) Variation Section 4.6 Update Dec 2025 - Proposed (**Replace**) (0006)			

Figure 5 (A4): Progression on the 2nd Parallel Proposal

In this example, as the procedure progresses, the proposed change to section 4.6 needs to be further amended as a result of the regulatory review (e.g. updated wording as suggested by the assessor), and this amendment is done with a replacement document in sequence 0007. Once a decision is reached, another sequence, 0008, is submitted, including the new decision replacing the one submitted in sequence 0006, and a deletion of the section 4.6 proposal, as amended by sequence 0007.

	MAA	**Approval**	**Variation 1**	**Variation 2**
0003 (rel sequence – 0000)		SmPC (English) Decision July 2025 **(Replace)**		
0004 (rel sequence – 0004)			Variation Section 4.4 Update July 2025 - Proposed (**New**)	
0005 (rel sequence – 0005)				Variation Section 4.6 Update August 2025 - Proposed (**New**)
0006 (rel sequence – 0004, 0005)		SmPC (English) Decision Dec 2025 **(Replace)**	Variation Section 4.4 Update July 2025 - Proposed (**Delete**)	Variation Section 4.6 + inclusion of approved Variation Section 4.4 Update Dec 2025 – Proposed (**Replace**)
0007 (rel sequence – 0005)				Variation Section 4.6 + inclusion of approved Variation Section 4.4 Update January 2026 – Proposed (**Replace**)
0008 (rel sequence – 0005)		SmPC (English) Decision Mar 2026 **(Replace)**		Variation Section 4.6 + inclusion of approved Variation Section 4.4 Update January 2026 – Proposed (**Delete**)
	eCTD Viewer Current View			
0000 - 0006	SmPC (English) Decision Dec2025 **(Replace)** (0006) Variation Section 4.6 Update Dec 2025 - Proposed (**Replace**) (0006)			
0000 - 0007	SmPC (English) Decision Dec 2025 **(Replace)** (0006) Variation Section 4.6 Update Jan 2026 - Proposed **(Replace)** (0007)			
0000-0008	SmPC (English) Decision Mar 2026 **(Replace)** (0008)			

A4-4.2.3 Approval of Multiple Variations at the Same Time

There will be occasions where multiple changes are approved at the same time, or within a very short time period. In these instances, it would not be appropriate to submit separate 'approved content for each variation; instead, a consolidated document representing all the approved changes should be submitted. This would replace the existing 'approved' content. The eCTD sequence containing the new approved content would also contain leaves deleting the relevant 'proposed' documents, as illustrated in Figure 5.

Figure 6 (A4): Replacement of approved content by newly approved content, and deletion of multiple proposed documents

In this example, EDA decision received in December 2025 incorporates the changes from the Variation submitted in sequence 0004, and also the changes from the Variation in sequence 0005. In sequence 0006, both 'proposed' documents from the variations are deleted and the new EDA decision is provided, replacing the original EDA decision from sequence 0003. This leaves only the latest EDA Decision from sequence 0006 in the current view. While creating a combined closing sequence covering multiple EDA Decisions is allowed, adding other regulatory activities into this closing sequence, e.g. to include a consolidation, is not acceptable.

	MAA	**Approval**	**Variation 1**	**Variation 2**
0003 (related sequence – 0000)		SmPC (English) Decision July 2025 (**Replace**)		
0004 (related sequence – 0004)			Variation Section 4.4 Update July 2025 - Proposed (**New**)	
0005 (related sequence – 0005)				Variation Section 4.6 Update August 2025 - Proposed (**New**)
0006 (related sequence – 0004 & 0005)		SmPC (English) Decision Dec 2025 (**Replace**)	Variation Section 4.4 Update July 2025 - Proposed (**Delete**)	Variation Section 4.6 Update August 2025 - Proposed (**Delete**)
	eCTD Viewer Current View			
0000 - 0005	SmPC (English) Decision July 2025 (Replace) (0003) Variation Section 4.4 Update July 2025 - Proposed (**New**) Variation Section 4.6 Update August 2025 - Proposed (**New**)			
0000 - 0006	SmPC (English) Decision Dec 2025 (**Replace**)			

A4-4.2.4 Rejections or Withdrawals

If any proposed changes are rejected or withdrawn by the applicant, then the applicant can provide a sequence deleting the "proposed" content document but not providing any replacement for the original approved document.

A4-4.2.5 Typical Applications

An applicant is most likely to need to submit parallel variations on dossier content that changes more often, such as the SmPC or the Risk Management Plan (RMP). However, this guidance is not limited to use in these parts of the dossier. Applicants should also note that many variations affecting the SmPC and RMP will not occur in parallel with another variation, and at times, when a variation is initially expected to be completed in isolation, a second parallel variation may become necessary at a later stage.

Annex 5 Section 1.2

Titles in *italics* are folders, containing subfolders but do not contain documents.

Table 7 Annex Document Table

Number	Title
1.2	*Application Forms*
1.2.1	Application Form
1.2.2	Legal Documents
1.2.2.1	Letter of Attorney for Company Representative
1.2.2.2	Manufacturing License and IDA License
1.2.2.3	GMP Certificate(s) / Alternative Documents
1.2.2.4	The Register of Trade
1.2.2.5	Toll Manufacturer License
1.2.2.6	Scientific Office License
1.2.2.7	Importers Register License
1.2.2.8	Store License
1.2.2.9	Authorisation Letter / Agency Agreement
1.2.2.10	Manufacturing Agreement
1.2.2.11	Packaging Agreement
1.2.2.12	Storage Agreement
1.2.2.13	Other Agreements
1.2.2.14	Termination / Waiver
1.2.2.15	Tax Card
1.2.2.16	List of Distributors
1.2.2.17	IP Protection Law No. 82 of 2002 Commitment
1.2.2.18	NEW local MA legal Agreement
1.2.2.19	Letter of Authorisation for a new Applicant in Egypt
1.2.2.20	PV Agreement between the MAH & the Service Provider
1.2.2.21	GMP Certificate
1.2.3	*EDA Approvals*
1.2.3.1	Registration Request Approval
1.2.3.2	Inquiry Approval
1.2.3.3	Name Approval
1.2.3.4	Registration License
1.2.3.5	Preliminary Approval

1.2.3.6	Non-Reference Approval
1.2.3.7	Exemption Approval
1.2.3.8	Pricing Certificate
1.2.3.9	Pharmacovigilance Approval
1.2.3.10	Inspection Report
1.2.3.11	Importation Approval for each API
1.2.3.12	CADC Report
1.2.3.13	Stability Study Approval
1.2.3.14	Stability Protocol Approval
1.2.3.15	Module 3 Approval
1.2.3.16	Module 5 Approval
1.2.3.17	Pre-approved letters from EDA concerning the product
1.2.3.18	Variation Approvals
1.2.3.19	Innovative Products Scientific Committee Approval
1.2.3.20	Registration License for the Solvent
1.2.4	*Declarations*
1.2.4.1	Declaration Letter stating the list of Registered & Under-Registration Products owned by the Toll Company
1.2.4.2	Declaration Letter from the License Holder specifying the API Manufacturers
1.2.4.3	Declaration letter from the license holder specifying approved pack in Egypt
1.2.4.4	Declaration Letter from the License Holder stating the Form of Bulk (Strips, Capsules, etc.)
1.2.4.5	Declaration Letter from the Manufacturer of the active substance to inform the Applicant in case of Modification of the manufacturing Process or Specifications
1.2.4.6	Declaration Letter from API Supplier
1.2.4.7	Declaration Letter for Site Addition
1.2.4.8	Declaration Letter Form LH stating all Variations & Justification for the Change
1.2.4.9	Other declarations requested by Egyptian Drug Authority
1.2.4.10	List of the Countries where the Product is registered & marketed
1.2.4.11	Ph. Eur. Certificate(s) of Suitability for TSE
1.2.4.12	TSE/BSE Supplier Safety Declaration (if CEP not available)
1.2.4.13	Raw Materials Storage Responsibility Declaration (for local Products)
1.2.4.14	Excipient/s Supplier Name & Origin
1.2.4.15	Trade Name of the Albumin used as Stabilizer
1.2.4.16	Albumin as Stabilizer Batch Release Certificate

1.2.4.17	Plasma Derivative Supplier Safety and Efficacy Commitment
1.2.4.18	No Change in physical Address and Product related Processes Declaration
1.2.4.19	Pack Type Declaration
1.2.4.20	Insert Declaration Letter
1.2.4.21	Site Master File Declaration
1.2.4.22	Storage Temperature at 25 °C Declaration
1.2.5	*Reference Product Document / Compendial*
1.2.5.1	The Reference Product Documents
1.2.5.2	Scientific Reference (Trials & Literature)
1.2.5.3	Reference for the trade name change
1.2.5.4	The latest recent Pharmacopeia
1.2.6	*Imported Products Documents*
1.2.6.1	Certificate of Pharmaceutical Product (CPP)
1.2.6.2	List of Affiliates / Subsidiaries
1.2.7	*Reliance Documents*
1.2.7.1	Sameness Letter
1.2.7.2	Unredacted Assessment Report
1.2.7.3	RRA Variation Application with Annexes
1.2.7.4	Correspondences between the Applicant and the Reference Agency
1.2.7.5	List of Changes after first MA issued from EMA or FDA
1.2.7.6	Rejection or Amendment Reporting Commitment
1.2.8	*Composition Documents*
1.2.8.1	Composition Certificate
1.2.8.2	Specifications
1.2.8.3	Any Composition Calculations
1.2.8.4	Pellets / Premix Composition and Certificates
1.2.8.5	Opadry / Coating Premix Composition
1.2.8.6	Capsule Shell Composition
1.2.8.7	Synonyms Evidence
1.2.9	Certificate of Analysis
1.2.10	*Post Approval Changes Requirements*
1.2.10.1	PAC Approval from the COO (Imported Products)
1.2.10.2	Summary of Change for Variation
1.2.10.3	Justification of the proposed Post Approval Change
1.2.10.4	Any additional Documents relevant to Variations

1.2.11	Proof of Payment
1.2.12	*Analysis Requirements Documentation (for Biological Products only)*
1.2.12.1	Detailed Standard Operating Procedures (SOP)
1.2.12.2	Summary Protocol for Vaccines and Plasma derived Medicinal Products
1.2.13	*For Plasma derived Medicinal Products*
1.2.13.1	Plasma Master File
1.2.13.2	Certificate of Plasma Batch Release from Health Authority
1.2.13.3	PMF Approval from Country of Origin
1.2.14	Scientific Advice Report
1.2.15	*Documents related PV*
1.2.15.1	Latest valid PSMF Assessment Report / Confirmation E-mail of PSMF Document(s) Receival
1.2.15.2	Updated Version of Summary of PSMF(s) / PSSF
1.2.15.3	The latest PSUR(s) (or the ACO in Case of Renewal)
1.2.15.4	The most updated EU/Global/Core-Risk Management Plan (RMP)
1.2.15.5	The Egyptian Display of EU-RMP / Global-RMP
1.2.16	*Documents related Inspection*
1.2.16.1	Site Master File for all Manufacturers
1.2.16.2	Latest Full Inspection Report(s) by SRA (past 3 Years)
1.2.16.3	One completed Batch Manufacturing and Packaging Record
1.2.16.4	List of any Recalls with Quality Defects (past 3 Years) (if found)
1.2.16.5	Any Warning Letter or equivalent regulatory Action (Production-line specific) (if found)
1.2.16.6	Last Annual Product Quality Review
1.2.16.7	Cold Chain Storage & Transportation Procedures including Excursion allowed

Annex 6: Controlled Vocabulary

EG Submission Type

EG Submission Types for Pharmaceuticals

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
maa	MAA	Marketing Authorisation Application	The applicant seeks approval from a regulatory authority that allows a pharmaceutical company to register and market a specific pharmaceutical product within Egypt and other countries.
var-pac-n	Var PAC-N	Variation PAC-N	Variations that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP and such changes can be implemented immediately at the time of submission, and they can be considered accepted by receiving a notification letter stating that the EDA is notified with the change.

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
var-pac-b	Var PAC-B	Variation PAC-B	Variations that may have minor effects on the overall safety, efficacy and quality of the FPP and such changes can be implemented when the variation is considered accepted and they can be considered accepted by receiving an inquiry Letter stating the required studies to be fulfilled in order to issue the Final Approval on the variation request.
var-pac-a	Var PAC-A	Variation PAC-A	Variations that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP and must be submitted annually and such changes do not require prior acceptance and can be implemented directly and the applicant must submit them collectively within 12 months from the date of implementation of the changes and they can be considered accepted by receiving a notification letter stating that the EDA is notified with the changes.
var-pac-ii	Var PAC-II	Variation PAC -II	Variations that could have major effects on the overall safety, efficacy and quality of the FPP and Such changes can be implemented when the variation is considered accepted and they can be considered accepted by receiving Inquiry Letter stating the required studies to be fulfilled in order to issue the Final Approval on the variation request.

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
renewal	Renewal	Renewal	The applicant submits the re-registration dossier containing the renewal requirements to obtain final re-registration approval
asmf	ASMF	Active Substance Master File	Submission used to provide detailed information about the active pharmaceutical ingredient (API) in a medicinal product
cep	CEP	Certificate of suitability	Submission that applies to an application on a Certificate of suitability CEP application (EDQM only) to demonstrate compliance with European Pharmacopoeia for active substance used in a product
none	none	none	In the exceptional case of reformatting the application no regulatory activity is allowed. Therefore, none' must be stated. The submission application unit will identify the sub-activity related to the product. In the submission description some information can be provided to e.g. highlight specific modules being reformatted.
preass	Pre-assessment	Pre-assessment	Refers to the process of evaluating or reviewing the application before the official or final assessment takes place.

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
pacstab	Post MA Commitments (Stability Studies)	Post MA Commitments (Stability Studies)	Refers to obligations or conditions concerning Stability Studies that must be fulfilled after the Marketing Authorization License is issued
paccadc	Post MA Commitments (CADC analysis)	Post MA Commitments (CADC analysis)	Refers to obligations or conditions concerning CADC analysis that must be fulfilled after the Marketing Authorization License is issued
paci	Post MA Commitments (Inspection)	Post MA Commitments (Inspection)	Refers to obligations or conditions concerning Inspection that must be fulfilled after the Marketing Authorization License is issued
pacqr	Post MA Commitments (Quality requirements)	Post MA Commitments (Quality requirements)	Refers to obligations or conditions concerning Quality requirements that must be fulfilled after the Marketing Authorization License is issued
5yr	Fifth Year Report	Fifth Year Report	A report on safety, quality and efficacy submitted by the applicant in the fifth year of the Marketing Authorization license otherwise the marketing of the product will be suspended. This process occurs every five years, during which the dossier is updated.

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
appeal	Appeals	Appeals	Refers to the process of requesting a formal review or reconsideration of a decision made by EDA. For registration, re-registration and under registration cases, the applicant submits the relevant documents based on the specific case registration.
preappinq	Preliminary Approval Inquiry	Preliminary Approval Inquiry	The applicant submits an application to receive preliminary approval to proceed with fulfilling the renewal requirements and studies

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General EG Submission Types for Biologics and Innovative Products

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
renewal	Renewal	Renewal	The applicant submits the re-registration dossier containing the renewal requirements to obtain final re-registration approval
none	none	none	In the exceptional case of reformatting the application no regulatory activity is allowed. Therefore, none' must be stated. The submission application unit will identify the sub-activity related to the product. In the submission description some information can be provided to e.g. highlight specific modules being reformatted.
pacstab	Post MA Commitments (Stability Studies)	Post MA Commitments (Stability Studies)	Refers to obligations or conditions concerning Stability Studies that must be fulfilled after the Marketing Authorization License is issued
paccadc	Post MA Commitments (CADC analysis)	Post MA Commitments (CADC analysis)	Refers to obligations or conditions concerning CADC/BioInn analysis that must be fulfilled after the Marketing Authorization License is issued

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
pacqr	Post MA Commitments (Quality requirements)	Post MA Commitments (Quality requirements)	Refers to obligations or conditions concerning Quality requirements that must be fulfilled after the Marketing Authorization License is issued
paci	Post MA Commitments (Inspection)	Post MA Commitments (Inspection)	Refers to obligations or conditions concerning Inspection that must be fulfilled after the Marketing Authorization License is issued
PMF	Plasma Master file	Plasma Master File	Submission of documentation for certification and re-certification of PMF related to blood/plasma-derived medicinal products / excipients.
withdrawal	Withdrawal	Withdrawal	Withdrawal of a marketing authorisation application entirely. This submission type shall not be used to withdraw a regulatory activity.

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EG Submission Types for Innovative Products

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
maa-inn	MAA-INN	Marketing Authorisation Application for an innovative product	The applicant seeks approval from a regulatory authority that allows a pharmaceutical company to register and market as an innovative product within Egypt
ipv-admc	IPV-ADMC	Innovative product variation - Administrative changes	For changes related to the administrative and the legal information, applicable for all innovative products
ipv-admlc	IPV-ADMIC	Innovative product variation - Administrative product labelling information changes	Editorial changes that are not expected to affect the safe and efficacious use of the product, applicable for all innovative products
ipv-tlc	IPV-TLC	Innovative product variation - therapeutic labelling information changes	For changes that have the potential to improve the management of risk to the population, applicable for all innovative products
ipv-pu	IPV-PU	Innovative product variation - pack update	For changes in outer carton and inner labels information, applicable for all innovative products

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
ipv-safeffc	IPV-SAFEFFC	Innovative product variation - safety and efficacy labelling changes	For changes that have an impact on the clinical use, applicable for all innovative products
imv-majvar	IMV-MAJVAR	Innovative medicinal products variation- Major variation	For changes that could have major effects on the overall safety, efficacy and quality of the API and FPP, applicable for all innovative medicinal products
imv-minvar	IMV-MINVAR	Innovative medicinal products variation- Minor variation	For changes that may have minor effects on the overall safety, Efficacy and quality of the API and FPP, applicable for all innovative medicinal products
imv-not	IMV-NOT	Innovative medicinal products variation- Notifications	For changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the API and FPP, applicable for all innovative medicinal products
ibv-majqualc	IBV-MAJQUALC	Innovative biological products variation-Major quality changes	For Changes that have significant potential impact on the quality, safety, or efficacy, applicable for all innovative biological products
ibv-modqualc	IBV-MODQUALC	Innovative biological products variation- Moderate quality changes	For changes that have moderate potential impact on the quality, safety, or efficacy, applicable for all innovative biological products

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
ibv-minqualc	IBV-MINQUALC	Innovative biological products variation-Minor quality changes	For Changes that have a minimal potential impact on the quality, safety, or efficacy, applicable for all innovative biological products
ibv-qcnoimp	IBV-QCNOIMP	Innovative biological products variation- Quality changes with no impact	For Changes that have no impact on product quality, safety, or efficacy, applicable for all innovative biological products

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EG Submission Types for Biologicals

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
maa-nt	MAA - Normal Track	Marketing Authorisation Application	applicable for all biological products
maa-ft	MAA - Fast Track	Marketing Authorisation Application for expedited review	applicable for certain products that are mentioned in eligibility criteria in the fast-track guideline
maa-sb	MAA - Second Brand	Marketing Authorisation Application for encouraging local production of brand products	applicable for products that have a manufacturing contract with the registered brand product in Egypt
maa-rl1	MAA - Reliance level 1	Marketing Authorisation Application for EMA/FDA products with unredacted assessment repot &/or LoQ	applicable for imported products with EMA/FDA CPPs
maa-rl2	MAA - Reliance level 2	Marketing Authorisation Application for EMA/FDA products with CTD only	applicable for imported products with EMA/FDA CPPs
maa-bios	MAA - Biosimilar	for biosimilar products only (products with comparability study to innovator)	for products manufactured according to biosimilar guidelines

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
np-modqualc	Normal pathway Moderate quality changes	Normal pathway Moderate quality changes	for Changes that have moderate potential impact on the quality, safety, or efficacy of the biotherapeutic product applicable for all biologicals products
np-pilc	Normal pathway Product labelling information changes	Normal pathway Product labelling information changes	for changes that have the potential to improve the management of risk to the population, applicable for all biologicals products, applicable for all biologicals products
np-majqualc	Normal pathway Major quality changes	Normal pathway Major quality changes	for Changes that have significant potential impact on the quality, safety, or efficacy of the biotherapeutic product applicable for all biologicals products
np-safeffc	Normal pathway Safety and efficacy changes	Normal pathway Safety and efficacy changes	for changes that have an impact on the clinical use of the biotherapeutic product, applicable for all biologicals products
np-admpilc	Normal pathway Administrative product labelling information changes	Normal pathway Administrative product labelling information changes	editorial changes that are not expected to affect the safe and efficacious use of the product, applicable for all biologicals products
np-packup	Normal pathway - pack update	Normal pathway - pack update	for changes in outer carton and inner labels information, applicable for all biologicals products

Abbreviation for EG Submission Types	EG eCTD M1 Submission Types	Submission Title	Description
np-adminc	Normal pathway - Administrative changes	Normal pathway - Administrative changes	for changes related to the administrative and the legal information of the biotherapeutic product, applicable for all biologicals products
rp-majcq	Reliance pathway-Major quality changes	Reliance pathway-Major quality changes	expedite procedure for major quality changes for product approved by RRA
rp-modqc	Reliance pathway-Moderate quality changes	Reliance pathway- Moderate quality changes	expedite procedure for moderate quality changes for product approved by RRA
rl-pilc	Reliance pathway - product labelling information changes	Reliance pathway - product labelling information changes	expedite procedure for labelling update for product approved by RRA
not-minqc	Notification-Minor quality changes	Notification-Minor quality changes	for Changes that have a minimal potential impact on the quality, safety, or efficacy of the biotherapeutic product, applicable for all biologicals products
not-qcnoimp	Notification- quality changes with no impact	Notification- quality changes with no impact	for Changes that have no impact on product quality, safety, or efficacy applicable for all biologicals products

EG Submission Modes

EG Submission Mode	Submission Mode Title	Submission Mode Description
Single	A Single Regulatory Activity	a single regulatory activity (e.g. a Type II variation)
Grouping	A Grouped Activity	**Human Pharmaceuticals** Several variations grouped to a single submission for a single product **Biological and Innovative Products** - Several variations grouped to a single submission for a single product Or - Several variations grouped into a single submission for multiple products Or - Single variation submitted for multiple products
Parallel Single	Parallel Assessment Single RA	Parallel Assessment For Imported Products, evaluation of the procedure at the same time with the authority of the country of origin.
Parallel Grouping	Parallel Assessment Grouped RA	Parallel Assessment For Imported Products, evaluation of the procedure at the same time with the authority of the country of origin.

EG Submission Unit

Submission Unit	Submission Unit Description	Notes
initial	Initial submission to start any regulatory activity	
validation-response	For rectifying submission in response to content validation issues.	
response	Submission Unit that contains the response to any kind of question, out-standing issues information requested by the agency. or used when consolidating the dossier as a result of withdrawing or rejecting a single regulatory activity.	• response for evaluation or • when consolidating the dossier as a result of withdrawing or rejecting a single regulatory activity (not in case of the withdrawal of the entire application). The "submission-description" should include some text to identify the sequence as a consolidation sequence after regulatory activity rejection/withdrawal.
additional-info	Other additional Information (could include, for example, missing files) and should only be used, if validation-response or response is not suitable	
corrigendum	Correction of information	The submission type 'corrigendum' should only be used in exceptional circumstances to correct information after the Regulatory Activity has concluded. Its use must be discussed and agreed with EDA in advance on a case-by-case basis.

Submission Unit	Submission Unit Description	Notes
reformat	Intended to support the reformatting of an existing submission application from any format to eCTD, i.e. a baseline eCTD submission	Intended to support the reformatting of an existing submission application from any format to eCTD, i.e. a baseline eCTD submission containing no content change and which will not be subject to review (see 2.11). This type will always be used together with the submission type '*none'*
re-examination	Used for requesting a re-examination of an authority opinion	Used for requesting a re-examination of an authority opinion (applicable for MAA, type II variation)

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History Table

Summary of Changes	Issue date	Version No.
New Issue		**1**

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