Industry Guidance on eCTD submissions to the World Health Organization's Prequalification Unit (WHO-PQT)

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1 DOCUMENT CONTROL

1.1 Change Record

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2 Contents

3 GLOSSARY

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

Term	Definition
Applicant	A pharmaceutical company or its agent submitting information in support of an application to WHO-PQT.
Application	A collection of electronic documents compiled by a pharmaceutical company or its agent in compliance with WHO-PQT guidelines in order to seek a product's prequalification or listing, or any changes thereof. An eCTD application may comprise a number of submissions or sequences.
Application Type	The application type describes the type of PQ assessment process to which the content will be submitted.
Dossier	A collection of electronic documents compiled by a pharmaceutical company or its agent in compliance with the WHO guidelines in order to seek a prequalification or listing recommendation or any amendments thereof.
eCTD backbone	XML, file and folder structure including technical files
eCTD identifier	An eCTD identifier is a name, code or number used as the directory name in the top-level directory. This can be a proposed trade name, a company internal project code, or the Marketing Authorization Number.
eCTD submission or sequence	A single set of information and/or documents in eCTD format supplied by the applicant as a partial or complete application.
Envelope	The envelope of Module 1 contains the metadata of the submission.
OP	Open Part of an APIMF
Regulatory Activity	Used to group together several related sequences of an application.
RP	Restricted Part of an APIMF
Salesforce Case ID	A Salesforce generated number, unique to the application submitted. It follows a simple 8 digit number format
Salesforce Product ID	Persistent Unique product record identifier, following the format P-XXXXX
Salesforce Portal	A Salesforce-based Community website, where applicants can lodge and monitor applications, products and a variety of other records.
Sequence	A single set of information and / or electronic documents submitted at one particular time by the applicant as a part of, or the complete application. Any collection of content assembled in accordance with the eCTD specification (ICH and WHO) will be described using metadata

	as defined by the WHO-PQT 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 will be used.
WHO Product ID	Changeable unique product identifier used by WHO-PQT. Format varies depending on product type. At the time of record creation the WHO Product ID is populated with the Salesforce Product, but this may change depending of the product type.

4 LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
API-PQ	Prequalified Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
CTD	Common Technical Document
DTD	Document Type Definition
eCTD	electronic Common Technical Document
FO	Form
FPP	Finished Pharmaceutical Product
FVP	Finished Vaccine Product
ICH	International Council on Harmonization
INN	International Non-Proprietary Name
LCM	Life Cycle Management
LoQ	List of Questions
NeeS	Non-eCTD Electronic Submission
OCR	Optical Character Recognition
PDF	Portable Document Format
PI	Product Information
PQ	Prequalification
Q&A	Questions and Answers document
ToC	Table of Contents
XML	Extensible Markup Language

5 INTRODUCTION

This document aims to provide guidance on submitting regulatory information in eCTD format to the World Health Organization (WHO) Prequalification Unit by Applicants.
It reflects the current situation and will be updated regularly to implement changes in WHO-PQT guidelines and/or ICH regulations.

The preparation and filing of submissions in eCTD format will be transitioned over a multi-year period. Commencing with voluntary eCTD submission and finally moving to mandatory submission and when applicable, the conversion of all legacy product dossiers to eCTD format. The eCTD webpage on the Prequalification Unit webpage will provide more detailed information on these timelines.

Applicants who choose to file a submission in the eCTD format must comply with the requirements as described in this document. Submissions and additional information in electronic format that do not comply with these requirements will fail during the dossier validation step and the applicant will be asked to resubmit.

Applicants are also encouraged to consult other guidance documents published by WHO and ICH. A non-exhaustive list can be found in Appendix 1 (chapter 10.1) for more information.

6 PURPOSE AND SCOPE

The purpose of this guidance document is to integrate the eCTD format into the WHO prequalification framework by describing the electronic format requirements for submissions and pursuant to all relevant guidance.

Information on the use of the WHO-PQT portal itself and the document submission process is not part of this guidance document. Please refer to the Prequalification Unit website for more information.

6.1 Types of products/submissions

This guidance document applies to Finished Pharmaceutical Products (FPPs), Finished Vaccine Products (FVPs) and Active Pharmaceutical Ingredients (APIs).

The eCTD format is also encouraged for the drug component of drug and device combinations, where the primary mechanism of action is drug related.

It does not apply to:

- veterinary medicinal products
- medical devices and drug-device combinations where the medical product combination is classified as a device
- notification procedures for complementary medicine
- notification applications for clinical trials.

6.2 Additional information and subsequent applications

Once an applicant files an application in the eCTD format, all additional information for the application and subsequent applications for the same medicinal product have to be filed in the eCTD format (“Once eCTD, always eCTD”). Applicants must not revert to a paper-based or NeeS format for subsequent applications for the same medicinal product.

In contrast, applications that pertain to a product that have not yet transitioned to eCTD must continue to be completed in NeeS format.

6.3 Filing formats of submissions in eCTD format

eCTD is considered to be an electronic only format. The current WHO-PQT procedures have to be taken into account to define which documents are needed for each submission type, and the documents detailed in Appendix 2 should be provided where applicable.

It is possible to submit eCTDs via the WHO-PQT portal. In doing so, it will not be necessary to submit any accompanying paper documents or discs by post, including wet signature documents. For more information on the portal, please refer to the WHO-PQT website.

7 TRANSFORMATION OF THE PAPER-BASED WHO-PQT CTD DOCUMENTATION TO THE DIGITAL WHO-PQT M1 ECTD SPECIFICATION

7.1 Purpose of this chapter

In the transformation process at WHO-PQT from CTD to eCTD some simplifications and changes have been made in order to take into account the different CTD requirements for Finished Vaccine Products, Finished Pharmaceutical Products and APIs. The goal was to create a single eCTD specification that combines all four products into a single eCTD specification.

7.2 Content of the Finished Vaccine Product eCTD

This section must be considered together with the requirements for CTD Preparation & Submission on the WHO-PQT website for vaccines. The business content in both guidelines – CTD and eCTD – are the same, however the numbering of the respective section has changed.

Transfer Number	ToC in CTD guideline	ToC Number in eCTD specification
01	1.0 Cover Letter	1.0
02	1.1 Table of contents	n.a.
03	1.2 Correspondence	n.a.
04	1.2.1 Letter of intention for submission	1.9.3
05	1.2.2 Pre-submission meeting minutes	1.9.1
06	1.3.1 Site Master File (SMF)	n.a.
07	1.4 Compliance information	1.10
08	1.4.1 Certificate of Establishment Licensing	1.10.1
09	1.4.2 GMP certificate and last GMP inspection report	1.2.5
10	1.4.3 Marketing authorizations or EMA scientific opinion for article 58 products	1.2.2
11	1.4.4 Policy for assignment of date of manufacture	1.10.2
12	1.4.5 Environmental Risk Assessment	1.10.3
13	1.5 Vaccine composition, presentations and scheduling information	1.11
14	1.5.1 Presentations available to UN agencies	1.11.1
15	1.5.2 Vaccine temperature stability profile	1.11.2
16	1.5.3 Description of immunization /administration devices to be delivered with the vaccine	1.3.4
17	1.5.4 Recommended schedule and route of administration	1.3.5
18	1.5.5 Artworks of primary containers and secondary packaging	1.3.2
19	1.5.6 Samples of package inserts	1.3.2
20	1.5.7 Template of lot summary protocol	1.11.3
21	1.5.8 PSPQ Self-assessment	1.11.4
22	1.6 Supplemental pre-clinical and clinical Information (Pre and post marketing)	1.12
23	1.6.1 Pre-clinical studies sponsored by applicant	1.12.1

24	1.6.2 Clinical trials sponsored by the applicant	1.12.2
25	1.6.3 Final approved protocol by ERC and NRA	1.12.3
26	1.6.4 Clinical trials currently ongoing	1.12.4
27	1.6.5 Other studies with applicant product for which the applicant is not the sponsor	1.12.5
28	1.6.6 Complementary Clinical summary	1.12.6
29	1.6.7 NRA(s) Assessment Report	1.12.7
30	1.6.8 Clinical Independent expert report	1.12.8
31	1.6.9 Post marketing Safety documentation	
32	1.6.9.1 Post-marketing pharmacovigilance or Risk Management Plan	1.8.2
33	1.6.9.2 Initial evaluation of vaccines that have been in the market for more than five years or reassessment of already prequalified vaccines	1.8.3
34	1.6.9.3 Ongoing clinical studies for vaccines licensed within the last five years	n.a.
35	1.7 Regulatory actions	1.13
36	1.7.1 Information on refusals, withdrawals, suspensions	1.13.1
37	1.7.2 List of lots rejected by an NRA	1.13.2
38	1.7.3 Restrictions on distributions and recalls of lots	1.13.3
39	1.7.4 Clinical trial suspensions	1.13.4
40	1.7.5 Dosage or schedule changes since initial marketing authorization	1.13.5
41	1.7.6 Changes in target populations since the initial marketing authorization	1.13.6
42	1.8 Distribution information	1.14
43	1.8.1 Quantity of finished product distributed in the domestic market	1.14.1
44	1.8.2 Countries where the product has received a Marketing Authorization	1.14.2
45	1.8.3 Release process by the NRA/NCL and recording system for distribution	1.14.3
46	1.8.4 Summary of the packaging procedures for international shipments for UN agencies and the validation	1.14.4
47	1.9 Responses to questions	1.15
48	1.10 Variations/ post-PQ changes	n.a.
49	1.10.1 Application form	1.2.1
50	1.10.2 Narrative description /Justification	n.a.
51	1.10.3 Responses to questions	1.15
52	1.11 Miscellaneous/Other documents	1.16
53	1.11.1 Post-PQ commitments	n.a.

Table 1: Conversion Table for FVP module 1 sections headings: CTD to eCTD

7.3 Content of the Finished Pharmaceutical Product eCTD

The content and numbering of a pharmaceutical product eCTD information required for submissions in eCTD format is the same as for WHO-PQT-CTD (e.g., Vaccine Prequalification Dossier - VPQD) submissions.

Section Number	Section Title eCTD guideline
1.0	Cover letter
n.a	Table of contents of the application including Module 1 (Modules 1–5)
1.2	Application information
1.2.1	Copy of the expression of interest (EOI)
1.2.2	Manufacturing and marketing authorization(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.3	Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP) (including any annexes)
1.2.4	Letters of access for active pharmaceutical ingredient master files (APIMFs)
1.2.5	Good manufacturing practices (GMP) information
1.2.6	Biowaiver requests in relation to conducting a comparative bioavailability study
1.2.7	Confirmation of API prequalification document (CPQ)
1.2.8	Contract manufacturing/testing/licensing agreements
1.2.9	Technology transfer protocol and reports/technology packs
1.2.10	Biosimilarity Claim
1.2.11	Summary of Changes Document
1.2.12	Previous Commitments
1.2.13	NRA approval
1.3	Product information
1.3.1	Summary of product characteristics (SmPC)
1.3.2	Labelling (outer and inner labels)
1.3.3	Package leaflet (also known as patient information leaflet or PIL)
1.4	Regional summaries
1.4.1	Bioequivalence trial information form (BTIF)
1.4.2	Quality information summary (QIS)
1.5	Electronic review documents (e.g., product information, BTIF, QIS, QOS–PD)
1.6	Samples (e. g. FPP, device(s), certificates of analysis
1.15	Response to Question
1.16	Other documents

Table 2: FPP Module 1 sections headings: eCTD

7.4 Content of the Active Pharmaceutical Ingredient Master File and Prequalified Active Pharmaceutical Ingredients eCTD

The content of PQ API and APIMF is essentially identical, varying only in the nature of the application form. The eCTD numbering of both API-PQ or APIMF is identical with the CTD structure seen in the Table 2: FPP Module 1 sections headings: eCTD.

Mandatory documents for initial PQ API and APIMF submissions are Cover Letter and Application Form.

7.5 Mandatory Documents for Finished Vaccine Products

Cover letter and Application form are mandatory for all Application Types and Application Sub-Types.

7.5.1 New Emergency Use Listing (EUL) Application, EUL, Full (EULF) and Product Extension (PEX)

Manufacturing Authorisations/Registrations/CPPs	Clinical studies sponsored by applicant
Good manufacturing practices (GMP) information	Final approved protocol by ERC and NRA
Summary of Product Characteristics (SmPC)	Clinical trials currently ongoing
Labelling Text and Mockups	Other studies, in support of WHO submission with the applicant product for which the applicant is not the sponsor
Package Leaflet, Description of immunization /administration devices to be delivered with the vaccine	Complementary Clinical summary
Recommended schedule and route of administration	NRA(s) Assessment Report
Post-marketing pharmacovigilance or risk management plan	Clinical Independent expert report
Initial evaluation of vaccines that have been in the market for more than five years or reassessment of already prequalified vaccines	Information on refusals, withdrawals, suspensions
Ongoing clinical studies for vaccines licensed within the last five years	List of lots rejected by an NRA
Presubmission meeting minutes	Restrictions on distributions and recalls of lots
Policy for assignment of date of manufacture	Clinical trial suspensions
Letter of Intention	Dosage or schedule changes since initial marketing authorization
Environmental Risk Assessment	Changes in target populations since the initial marketing authorization
Presentations available to UN agencies	Quantity of finished product distributed in the domestic market
Vaccine temperature stability profile to support prequalification	Countries where the product has received a Marketing Authorization
Template of lot summary protocol	Release process by the NRA/NCL and recording system for distribution
Pre-clinical studies sponsored by applicant	Summary of the packaging procedures for international shipments for UN agencies and the validation
Clinical studies sponsored by applicant	

Table 3: Mandatory documents for FVP New Emergency Use Listing (EUL) Application, EUL, Full (EULF) and Product Extension (PEX) applications

7.5.2 New Prequalification Application (Standard)

The same documents as New Emergency Use Listing (EUL) Application, EUL, Full (EULF) and Product Extension (PEX) and additionally:

- Certificate of Establishment Licensing
- PSPQ Self-assessment

Note: NRA(s) Assessment Report is not mandatory for New Prequalification Application (Standard) applications.

7.5.3 New Prequalification Application (Abridged)

Same documents as New Prequalification Application (Standard) but in addition the NRA(s) Assessment Report.

7.5.4 New Prequalification Application (Product Extension)

Summary of Changes Document
NRA approval
Summary of Product Characteristics (SmPC)
Labelling Text and Mockups
Description of immunization /administration devices to be delivered with the vaccine
Description of immunization /administration devices to be delivered with the vaccine, Recommended schedule and route of administration and Presentations available to UN agencies

Table 4: Mandatory documents for FVP New Prequalification Application (Product Extension)

7.5.5 Reassessment

Manufacturing Authorisations/Registrations/CPPs
Good manufacturing practices (GMP) information
Summary of Product Characteristics (SmPC)
Labelling Text and Mockups
Package Leaflet
Description of immunization /administration devices to be delivered with the vaccine
Recommended schedule and route of administration
Presubmission meeting minutes
Certificate of Establishment Licensing
Policy for assignment of date of manufacture
Environmental Risk Assessment
Presentations available to UN agencies
Template of lot summary protocol
PSPQ Self-assessment
Information on refusals, withdrawals, suspensions
List of lots rejected by an NRA
Restrictions on distributions and recalls of lots
Currently suspended clinical trials
Dosage or schedule changes since initial marketing authorization
Changes in target populations since the initial marketing authorization

Quantity of finished product distributed in the domestic market
Countries where the product has received a Marketing Authorization
Release process by the NRA/NCL and recording system for distribution
Summary of the packaging procedures for international shipments for UN agencies and the validation

Table 5: Mandatory documents for FVP Reassessment Applications

7.5.6 Post-PQ Change (Minor) and Post-PQ Change (eCTD Baseline)

In addition to Cover Letter and Application form, the Summary of Changes Document is required.

7.5.7 Post-PQ Change (Major)

In addition to Cover Letter and Application form, the Summary of Changes Document and NRA Approval is required.

7.5.8 Annual Report

The Annual Report requires only Cover Letter and Application Form as mandatory documents.

7.6 Mandatory Documents for Finished Pharmaceutical Products

Cover letter and Application form are mandatory for all Application Types and Application Sub-Types with the exception of Requalification Application where Application form is optional.

The mandatory documents for the combination of Product Sub-Type, Application Type and Application Sub-Type are listed in the following.

7.6.1 Product Sub-type BTP. New Prequalification Application (Full)

Manufacturing Authorisations/Registrations/CPPs
Good manufacturing practices (GMP) information
Contract manufacturing/testing/licensing agreements
Technology transfer protocol and reports/technology packs
Technology transfer protocol and reports/technology packs
Biosimilarity Claim
Summary of Product Characteristics (SmPC)
Labelling Text and Mockups
Package Leaflet
Quality information summary (QIS)
Editable review documents
Product Samples Details
Biosimilarity information summary
Pharmacovigilance system
Risk-management system and prequalification-specific addendum to the risk management plan
Summary of the packaging procedures for international shipments for UN agencies and the validation

Table 6: Mandatory documents for FPP Product Sub-type BTP, New Prequalification Application (Full)

7.6.2 Product Sub-type FPP. New Prequalification Application (Full); New Emergency Use Listing (EUL) Application (Full) (EULF)

Manufacturing Authorisations/Registrations/CPPs
Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP) (including any annexes)
Letters of access for active pharmaceutical ingredient master files (APIMFs)
Good manufacturing practices (GMP) information
Biowaiver requests in relation to conducting a comparative bioavailability study
Confirmation of API prequalification document (CPQ)
Contract manufacturing/testing/licensing agreements
Technology transfer protocol and reports/technology packs
Summary of Product Characteristics (SmPC)
Labelling Text and Mockups
Package Leaflet
Bioequivalence trial information form (BTIF)
Quality information summary (QIS)
Editable review documents
Product Samples Details

Table 7: Mandatory documents for FPP Product Sub-type FPP. New Prequalification Application (Full); New Emergency Use Listing (EUL) Application (Full) (EULF)

7.6.3 Product Subtype BTP. New Emergency Use Listing (EUL) Application (Full) (EULF)

The same documents as “Product Sub-type FPP. New Prequalification Application (Full); New Emergency Use Listing (EUL) Application (Full) (EULF)” and in addition:

- Pharmacovigilance system
- Summary of the packaging procedures for international shipments for UN agencies and the validation
- Risk-management system and prequalification-specific addendum to the risk management plan

7.6.4 Product Sub Type FPP and BTP. Requalification Application

The mandatory documents for requalification applications are as follows:

- Quality information summary (QIS)
- Product Samples Details
- Editable review documents

An application form is optional.

7.6.5 All FPP Post-PQ Change applications

Cover Letter and Application Form are mandatory for all Post-PQ changes for FPPs.

7.7 Mandatory Documents for APIMFs and API-PQ applications

The mandatory documents for all applications for APIMF and API-PQ products are Cover Letter and Application Form.

8 STRUCTURE AND CONTENT OF SUBMISSIONS IN ECTD FORMAT

8.1 Structure

The content of information required for submissions in eCTD format is the same as for non-electronic CTD submissions. However, the location of files may have changed in some situations (see sections 5.2 to 5.4).

The XML backbone reflects the eCTD structure. It can be viewed in any XML editor. Figures 1 and 2 illustrate part of the eCTD structure, as seen when using a review tool or a file explorer.

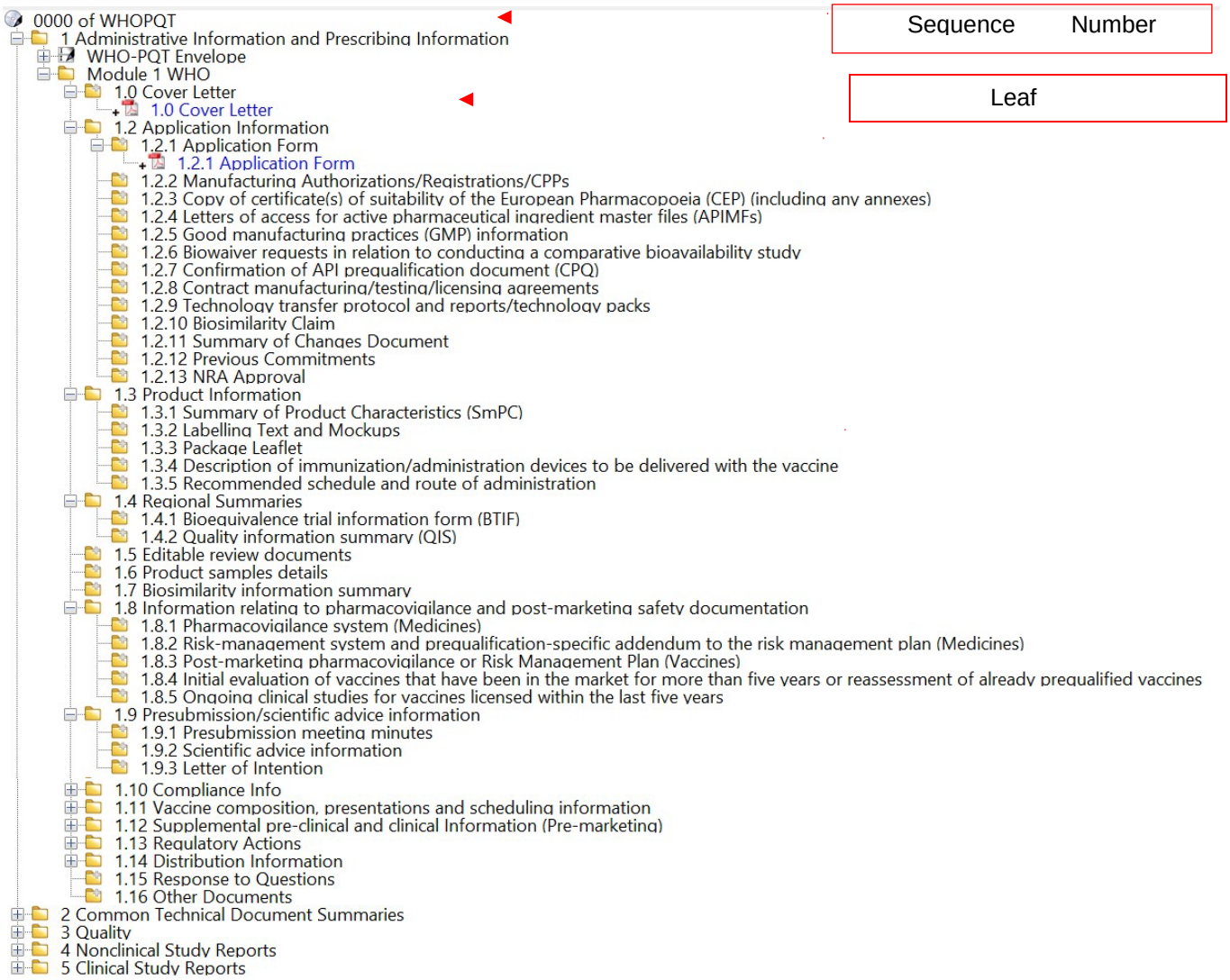

Figure 1 WHO eCTD ToC in an eCTD review tool

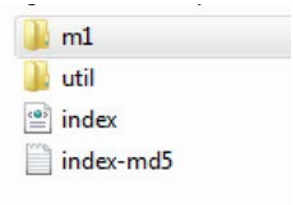

Figure 2: Example eCTD structure in file explorer view

The structure of an eCTD will affect the life cycle management of the eCTD over time, and therefore the structure of the first eCTD for a product or product range needs careful consideration.

8.1.1 eCTD Identifier

There is no requirement to use an identifier for the directory name in the top-level directory. However, in order to facilitate the handling of submissions, WHO-PQT recommends using the proposed INN name or a company internal project code as an identifier. Once defined, it should remain unchanged during the whole life cycle.

8.1.2 Sequence number folder

All files and folders in a submission in eCTD format are to be placed under the sequence number folder, as described in the *ICH Electronic Common Technical Document Specification, File Names and Directory Structure.*

The sequence number folder includes an m1 subfolder, m2–m5 subfolders (optional), and a *util* subfolder (see Figure 1). The eCTD backbone file (index.xml), the checksum file (index-md5.txt) and the util subfolder have to be placed in the sequence number folder as well. This sequence number folder must be named using a four-digit number, where for the first submission 0000 must be used. Subsequent submissions have to be provided using an incremental number, unique for each new sequence. Gaps between sequence numbers or disordered submissions should be avoided, i.e. sequence 0001 should be followed by 0002 and 0003 etc.

If a submission fails technical validation due to a technical error, the sequence number does not change when the submission is filed again (replacement sequence). If the submission passes technical validation, but has content deficiencies, resolving these deficiencies requires a new submission with a new sequence number (correctional sequence).

If one of several sequences simultaneously submitted fails technical validation, WHO-PQT accepts the correct sequences and asks for replacement of the invalid sequences, provided that no life cycle issues are present. This is subject to WHO-PQT's assessment on a case by case basis.

8.1.3 util and dtd subfolders

The *util* folder contains a *dtd* subfolder as well as a style folder and they must only contain the files that are mentioned in the WHO-PQT Module 1 Specification which define the regional module 1 backbone file. The *dtd* subfolder located in the root folder must only contain the ICH eCTD DTD that defines the eCTD backbone file. The style folders must contain the relevant style sheet information.

8.1.4 Module 1 subfolder

The content of the Module 1 is described in detail in the *WHO-PQT M1 Specification for eCTD* document.

8.1.5 Modules 2 to 5 subfolders

The structure and content of the modules 2 to 5 subfolders (m2–m5) are defined in the *ICH Electronic Common Technical Document Specification*. The following requirements are to be considered:

- Node extensions are allowed, but should only be used where necessary
- Node extensions are necessary for each clinical study report. The leaf title for the node extension should serve as study identifier, containing study number and appropriate study title. If clinical study reports consist of several PDF files, the leaf title of each file should indicate its content (e.g. “study number_synopsis”, “study number_main body” and “study number_ individual appendice”)
- The use of Study Tagging Files (STF) is not accepted and an eCTD containing STFs must be reworked for a submission for WHO-PQT.

8.2 eCTD Envelope

The metadata provided by the applicant with the eCTD are important, since they indicate relationships between individual sequences for effective life cycle management of the application. The particular envelope elements used by the review tool for display and management of submissions are listed in the *WHO-PQT Module 1 Specification for eCTD, Appendix 1*. Applicants must include and present metadata in a manner that unequivocally ties them to a submission (e.g. applicant name, INN). Over the life cycle of a medicinal product, metadata may only be changed for legitimate reasons (e.g. change of Applicant) and only if the change is technically supported. Consistency, quality and accuracy of metadata should always be assured.

The field *sequence description* is a free text field with a maximum of 180 characters possible. It serves to link the application number to the application (in case of more than one application per eCTD Sequence.

Using the *submission description* element, submissions relating to multiple parallel variations can be easily identified and grouped together. The contents of the *submission description* element should therefore be concise but clearly indicative of the substance of the application in question.

The *sequence description* can also serve to determine the differences between sequences where the same value for *application type* is used for multiple submissions. As an example, *new indication* as application type is not descriptive enough for the content and therefore the description should be supplemented by *application for new indication breast cancer* in the *submission description* field.

8.3 Metadata

The leaf attribute metadata provided by the applicant are considered important, since this information is displayed by review tools and is used for identifying documents and sections. The metadata become particularly important in managing the life cycle of the submission. For example, the *ICH eCTD Specification Document* describes six eCTD heading element attributes to structure the eCTD content. Five of these attributes can be found in Module 3:

- Substance
- Drug Product/Drug Substance Manufacturer
- Product Name
- Dosage Form
- Excipient

These attributes correspond to elements in the eCTD that may be repeated and are used to define specifically what each repeated section covers.

For example, in an eCTD submission covering two active ingredient manufacturing sites, the directory structure for the eCTD may be split into two paths which contain documents for the different sites. The XML should then be similarly structured (see *ICH eCTD Specification document*). The extent to which a single eCTD sequence can cover multiple substances, manufacturers, products and excipients, and the use of the respective attributes to describe what is being covered with, is left to the discretion of the applicant. eCTD sequences can be structured in various ways, affecting the presentation in the review tools and the repositories that are used to store the eCTD files and folder structure.

8.4 Inclusion of non-eCTD correspondence documentation

The term correspondence applies to all documents that are exchanged between the applicant and WHO-PQT in the context of prequalification procedures but which do not have a formal designated placeholder within the eCTD structure and/or are currently not supported in eCTD. For example, responses to WHO-PQT questions are not classified as correspondence since the WHO-PQT M1 eCTD DTD includes a designated section for such information.

Correspondence that is not directly relevant to the life cycle should be handled outside the life cycle,

e.g.: announcing the timeline for when the applicant will submit the responses to the List of Questions; requesting to extend a due date (e.g. for responses to List of Questions or to preliminary decisions);

However, any information that relates directly to the dossier content should be sent as an eCTD submission to WHO-PQT. This includes all changes and all annexes to the dossier sent as additional information, as well as the acknowledgement of final changes to details submitted in the body of the dossier.

8.5 Cover Letter

The cover letter is located in section 1.0 of the WHO-PQT Module 1. It has no life cycle and should therefore always be submitted with the document operation attribute *new*. As eCTD viewing tools display all *new* leaf elements in a current or cumulative view, it is recommended to place additional descriptive text in the leaf title to help identifying each cover letter leaf and the submission it is in. Some examples of possible leaf titles:

Cover Letter for New Indication AML Cover Letter Label CDS 01-Jan-2001

In case of a technical rejection, the original cover letter must be included alongside the new cover letter in the replacement sequence. The leaf titles of both cover letters should be named accordingly.

9 TECHNICAL REQUIREMENTS FOR SUBMISSIONS

9.1 Submission portal

Submission to WHO-PQT are submitted via WHO-PQT portal. For more information on the possibility to submit eCTDs using the WHO-PQT Portal please refer to the *WHO-PQT Website*.

9.2 Compression and password protection/security settings

The applicant is required not to apply any compression to the files inside the submission.
The submission needs to be compressed as ZIP-file for upload to WHO-PQT Portal.

One-time security settings or password protection of electronic submissions for security purposes are *not* acceptable during transportation from the applicant to WHO-PQT. Applicants should also *not* apply any file-level security settings or password protection to individual files in the eCTD. The file settings should allow printing, annotations to the documents, and selection of text and graphics.

The following requirements should be noted in relation to security:

- Encryption is not considered necessary when using physical media. The applicant should assume all responsibility for the media until it is delivered to WHO-PQT.
- Once received by WHO-PQT, security and submission integrity is the WHO-PQT's responsibility.
- The md5 checksum allows the recipient of the eCTD to ascertain whether files in the submission have been modified since the applicant generated the checksum.

9.3 PDF files

The following requirements apply in relation to PDF files:

- Files should be created according to the latest EWG M2 Recommendations and should be legible with the Acrobat Reader or any other viewer. PDF files should be saved as optimised to reduce the size and allow faster opening.
- PDF v1.3 or earlier are not acceptable for technical reasons. No exceptions will be made.
- The use of additional software to navigate and work with the files is not acceptable.
- Documents in PDF/A format are accepted. Documents in PDF/X format are only accepted if they do not interfere with the review functionality since this format does not support hyperlinking or bookmarks. Please liaise with WHO-PQT before including such PDF files.
- PDF files produced from an electronic source document are preferred to PDF files generated from scanned paper since these PDF files provide the maximum functionality to the reviewers in terms of search capabilities and copy & paste functionality. However, the PDF files of documents which bear an original signature on the paper version must be generated by scanning (e.g. cover letter, forms).
- Expert Reports and the Overviews/Summaries in Module 2 must be generated from an electronic source document.
- If scanning is unavoidable, readability and file size should be balanced; the following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid grayscale or colour where possible, use only lossless compression techniques.
- The maximum individual acceptable file size is approximately 200 MB. The file size should ensure clarity, speed of download and ease of review.
- All fonts used in a document should be embedded in the file.
- Adobe Portfolio files must not be used.

Additional details on PDF can be found in the *ICH eCTD Specification Document, App. 7*.

9.4 File naming conventions

It is recommended to adhere to the eCTD file naming conventions as described in the *ICH eCTD Specification Document*, the *WHO-PQT Module 1 Specification* and the *Validation Criteria*.

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

9.5 Hyperlinks and Bookmarks

In general, hyperlinks are encouraged within the eCTD to facilitate swift navigation within the dossier but should not be overused. They are only to be included where considered necessary and where they add real value. It is important that eCTD titles (i.e. the backbone entries visible as the eCTD ToC) are used in consistency with how the documents themselves are referred to within other documents, for example summary documents. Hyperlinks are needed if the title presented by the review tool in the eCTD ToC and the reference in a summary document do not match and therefore the backbone cannot be used. The eCTD should be structured, and links be provided in such a way as to ensure that the reviewer is constantly aware of the overall structure and narrative flow of the dossier.

For example, Module 3 is highly structured and defined to a relatively low level of granularity in the specification. Therefore, only minimal use of hyperlinks should be necessary. For example, when the same citation appears on a page more than once, it is recommended that a link only to the first instance of the citation per page be provided. Documents should be placed only once in the eCTD folder structure and referred to via hyperlinks.

In the nonclinical/clinical part of the eCTD, the structure is defined using a higher level of granularity. Within Modules 4 and 5, the localisation of studies and references may vary across submissions. For fast orientation purposes, linking from leaf to the respective part of the overviews and from overviews to Modules 4 and 5 is crucial (*two-click-strategy*). Hyperlinks from the nonclinical and clinical overviews to the references themselves can be provided directly from the text or from the list of references at the end of the document. Missing hyperlinks may lead to a formal objection.

Broken links are technically classified as best practice criteria (BP). Even though a submission is technically accepted, the submission may be objected due to formal reasons, if for example hyperlinks or bookmarks are not functional to a critical extent. As a general conclusion, broken links in a summary document (e.g. preclinical overview) are more critical than broken links in a study appendix due to different frequency these hyperlinks are used.
References should not contain external links (e.g. links to websites).

Within Modules 2 to 5, bookmarks are needed for documents larger than 20 pages, except for literature references where bookmarks are not necessary. In general, for documents with a table of contents, bookmarks for each item listed in the table of contents should be provided including all tables, figures, publications, other references, and appendices. For further information regarding the use of bookmarks, please refer to *ICH eCTD Specification Document.*

9.6 md5 checksum

md5 checksums are used to verify the integrity of physical files in the submission. Both the XML backbone and each file in the sequence will be checked using an individual checksum.

Applicants must place a checksum file named *index-md5.txt* in the same directory as the XML eCTD instance.

An invalid checksum will result in the rejection of the eCTD submission.

9.7 Editable Review Documents

WHO-PQT requires editable documents (section 1.5) (Word documents (.doc or .docx)) for some documents in for the purposes of review and document manipulation.

For documents with several versions during the review process, a date of the version should be included in the file name for tracking purposes and the following naming convention could be applied.

9.8 Virus check

The applicant is responsible for checking the submission for viruses. Checking should be performed with an up-to-date virus checker.

WHO-PQT will still perform an internal virus check after reception. A positive check will result in a rejection of the eCTD.

9.9 Technical validation before submission

WHO-PQT requires applicants to use a validation tool that checks the submission for technical interoperability before submission.

It is at the discretion of the applicant to provide best practice comments on the *Technical Validation eCTD - Part1* available on the WHO-PQT website. If submitted, the comments arenot part of the eCTD Module 1 and therefore must not be integrated in the eCTD but be submitted only as paper copy.

Further details on the validation are described in the document *WHO-PQT eCTD Validation Criteria*.

9.10 Handling of thumbs.db files

It is possible that *thumbs.db* files are present among the eCTD files after having published the sequence. *thumbs.db* files are system files created by Microsoft Windows (for versions before Windows 10) every time a file is opened and are often not displayed in the Windows Explorer. In the context of an eCTD submission such files are unreferenced in the XML backbone and will cause a validation error.
These sequences will be rejected, and a replacement sequence must be submitted.

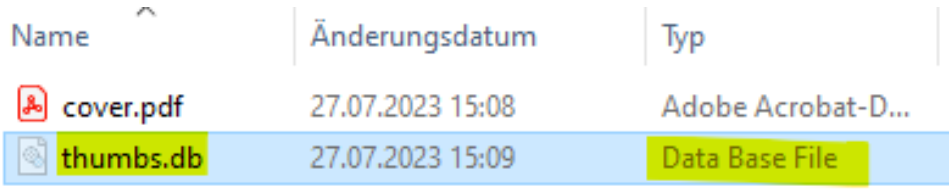

Figure 3: Example screenshot indicating the presence of the thumds.db file

To avoid creating thumbs.db files, the applicant is advised not to open files or folders after publishing and before burning the sequence on CD. It is possible to disable thumbs.db files in Microsoft Windows. Please liaise with your IT department for support.

10 LIFE CYCLE MANAGEMENT

10.1 Benefits of the Life cycle

Maintaining a life cycle offers several benefits such as traceability and transparency. For the ease of review, changes to submissions and documents are placed in the context of previous submissions, which makes it easier to find and compare changes. Review tools allow a current view, which represents the current status of the medicinal product and all documents.

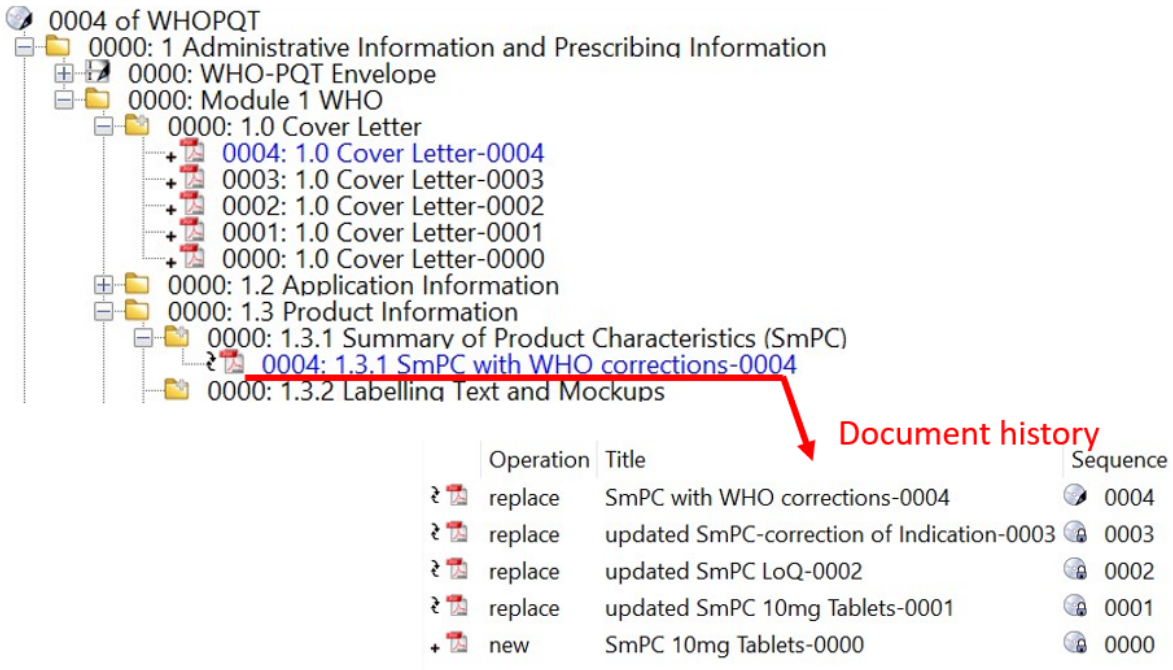

Figure 4: Example screenshot highlighting the use of document lifecycles

10.2 Life cycle management at the submission layer (i.e. eCTD sequence)

10.2.1 Metadata (Envelope)

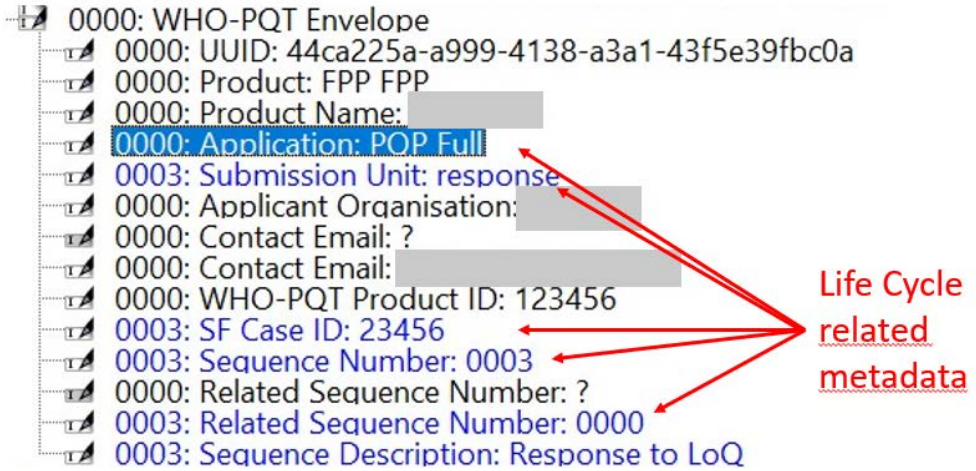

Figure 5: Example screenshot highlighting lifecycle metadata

10.3 Life cycle management at the document layer (eCTD leaf)

10.3.1 Leaf life cycle operation attributes

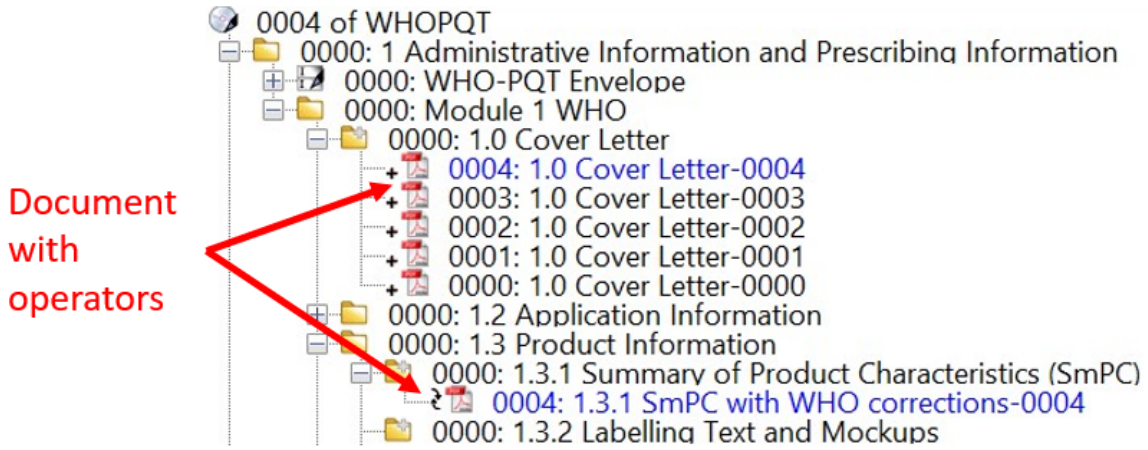

Figure 6: Example screenshot highlighting document operators

The operation attribute describes the relationship between leaf files in submissions subsequent a specific submission and in additional information related to those submissions (For an initial submission only the operation attribute *new* is applicable).

The four LCM activities (operation attributes) provided by the ICH are *new*, *replace*, *delete* and *append*. The operation *append* should be avoided due to potential LCM issues.

Further information can be found in the ICH Electronic Common Technical Document Specification.

10.4 Responses to the List of Questions

The document which lists all the questions with the corresponding narrative text response for each question should be placed in the *Responses section* of M1. It is also possible to split this document into multiple documents, for example one for answers to quality, nonclinical, and clinical.
For responses which contain new or updated data/documents relating to Modules 3-5, such data/documents have to be placed in the relevant sections of these modules. This may also apply to Module 1 (e.g. revised product information), as well as to Module 2 in cases where extensive data/documents would require the inclusion of the relevant summaries and/or overview sections.

If new or updated documents are required, hyperlinks from the consolidated LoQ document to the new or updated records in the eCTD dossier should be included.

10.5 Consolidation Sequences

10.5.1 Withdrawn, fully or partially rejected applications

These applications should not appear in the current view of the eCTD. If a submission is withdrawn or rejected, a consolidation sequence should be submitted to rebuild the approved status by removing eCTD documents associated with the rejected or withdrawn submission. The administrative documentation in Module 1 should be left unchanged (unless this documentation has an existing life cycle and is affected by the rejected or withdrawn variations). If you are unsure, please liaise with the responsible Case Manager.

The submission unit type should be *response* and the *related sequence* should match the initial sequence number

of the regulatory activity concerned or the sequence prior to the rejected or withdrawn application/variation, respectively.

10.6 Baseline submissions

10.6.1 General requirements

A baseline submission marks the change from a non-eCTD submission to an eCTD submission. Following a transition period (see PQT website) eventually all new and legacy products will be expected to be in eCTD format.

There is no requirement for a chronological or cumulative presentation of the dossier content in a base-line submission. The baseline submission should reflect the most recently approved details. A signed declaration must also be submitted as an annex to the cover letter stating that the content of the submitted eCTD is identical to the current approved documents and that there have been no changes to the dossier content as a result of the provision of the eCTD submission. It is not acceptable to exclude any information from the original dossier unless it has been updated by an approved PQT regulatory process (e.g. variation, line extension etc.).
The baseline should contain electronic source documents, but WHO-PQT also accepts scanned documents where OCR has preferably been applied to.

Only a technical validation will be performed on the eCTD sequence. There is no content validation and no in-depth review process involved. Acceptance of the baseline dossier does not imply acceptance of the details in the dossier.

The envelope element application type for a baseline submission should be ‘Post-PQ change’, application sub-type ‘eCTD Baseline’ and submission unit type ‘reformat’.

A baseline always has always to be submitted as a separate sequence.

The following has to be considered when preparing a baseline submission:

1) ***Timing of the submission:***

- Preferably as sequence 0000
- The baseline should always be a separate submission and should never include new changes.
- Ideally, the baseline should be submitted during a period when there are no other on-going applications for the product.
- Ideally, the applicant should wait to receive confirmation of the acceptance of the baseline submission before undertaking further regulatory action on the dossier.

2) ***Minimum requirement for a baseline***

- Baseline for Finished Pharmaceutical Products must contain M1 to M3 documents and it is recommended that it contains also module 4 and 5 documents if possible.
- Baseline for Finished Vaccine Products must contain M1 to M3 documents and it is recommended that it contains also module 4 and 5 documents if possible.
- Baseline for APIMFs (API-PQs) must contain M1 to M3 documents.
- Contain the latest approved documents

Navigation (Hyperlinks)*:* see section 8.5 but normally, no hyperlinking is necessary for a baseline sequence.

11 ADVICE ON SPECIFIC APPLICATION TYPES

11.1 API-PQ/APIMF in eCTD format

The following requirements have to be considered for electronic submission of APIMFs to WHO-PQT:

The APIMF to WHO-PQT should contain the restricted part and the open part and is submitted in eCTD format as part of Module 2 and 3.

APIMFs can be provided in support of an FPP product application from another manufacturer, and or API Prequalification applications by the API manufacturer themselves.

For the purposes of an FPP application, the eCTD APIMF dossier is treated as a stand-alone dossier and is independent of the FPP eCTD dossier. The APIMF (APIMF Holder, substance name) and the FPP (Applicantr, tradename) consist of two individual eCTD life cycles.

For the purposes of API-Prequalification, since an API-PQ product only ever refers to the corresponding APIMF product's documentation, a separate document repository for API-PQ products will not be put in place. Rather, all eCTD documents will be filed under the associated APIMF product record in the eCTD repository.

Meaning, API-PQ application lifecycles, like a APIMF Post-Prequalification Change application, will be treated as a sequence of the associated APIMF product dossier. Although the application form would vary, the module 3 remains common.

Example 1: Application for API-PQ is filed subsequently to the originally submitted APIMF

Sequence	Regulatory Action
0000	Application for a New APIMF Procedure
0001	APIMF amendment
0002	Application for API PQ (Conversion)
0003	APIMF amendment

Example 2: Application for API-PQ is filed with a new APIMF as part of the application

Sequence	Regulatory Action
0000	Application for API PQ
0001	APIMF amendment
0002	APIMF amendment
0003	APIMF amendment

11.2 Site Master File

Site master file is not part of the eCTD.
The site master file will typically be requested directly from the WHO-PQT inspectorate at the time of their site review.

12 APPENDICES

12.1 Appendix 1: eCTD Reference Documents

WHO-PQT
Guidance for Industry on Providing Regulatory Information in eCTD Format (this document) WHO-PQT eCTD Module 1 Specification
WHO-PQT eCTD Validation Criteria
Questions and Answers to WHO-PQT eCTD implementation

ICH
ICH: https://www.ich.org
ICH electronic Common Technical Document - eCTD v3.2.2: https://ich.org/page/ich-electronic- common-technical-document-ectd-v322-specification-and-related-files