ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)

eCTD HOW TO DO DOCUMENT

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INTRODUCTION

eCTD is a topic of increasing interest in the pharmaceutical environment. In the past, the main focus for regulatory authorities was eCTD submissions sent via MAAs. As a result, introduction of eCTD by API manufacturers was slow with limited eCTD guidance for API dossiers.

In recent times, however, the number of eCTD submissions for API manufacturers has increased (the FDA have reported an increase of eCTD submissions year on year) and guidance documents have been published that make it possible to create and maintain API dossiers using eCTD. API manufacturers are also beginning to understand the benefits from the adoption of eCTD.

This document will focus on eCTD only as it is considered the upcoming standard for electronic submissions. There are other options for electronic submissions such as NeeS (Non eCTD electronic Submission) in Europe or a single pdf-file. However, these submission types are not ICH-standard so their uses are limited when dealing with customers in different regions.

It must be noted, however, that when it comes to eCTD submission, there continues to be differences among different countries and even ICH regions. For example, the FDA began accepting eCTD submissions in 2003; Japan began accepting in 2004, yet the EU Heads of Medicines Agencies committed themselves, in 2005, to be ready for eCTD submissions by 2010. The approach of the different health authorities also continues to be different. For example, Japan has accepted eCTD since 2004 but eCTD submissions of API dossiers are not possible; in Europe, some agencies continue to require paper submissions for specific sections.

Outside the ICH region, countries are continuing to adopt the eCTD initiative and there is potential for eCTD to become the standard for non-ICH countries.

Chapter 1 of this guideline document discusses region and country-specific requirements for eCTD submissions, in particular the requirements for Module 1 of the dossier. These requirements are subject to change so this chapter should be considered as 'living' and will evolve over time to include additional countries when further eCTD guidance is published.

Chapter 2 gives an overview of the 3 main ways in which a company can adopt eCTD. The advantages and disadvantages of introducing eCTD in-house or via a host server or to fully outsource eCTD are discussed.

Chapter 3 goes further and describes the requirements necessary for an 'eCTD ready' API dossier.

Please note that this guideline document focuses entirely on the first submission of an API dossier. Lifecycle activities are not considered. However the reader should understand that submission management of products throughout their lifecycle is a key aspect and needs to be considered from the very beginning.

The authors hope this document will give the reader a basic understanding of eCTD, an understanding of the eCTD requirements expected by different Health Authorities and allows the reader to make an informed decision on how to implement eCTD.

1 CHAPTER 1: REGULATORY FRAMEWORK & NATIONAL REQUIREMENTS

1.1 Introduction: View of Authorities in General

The following chapter summarises the current format requirements for eCTD submission of DMF/ASMFs in the ICH countries (Europe: EDQM, EMA, national authorities, USA, Japan) and Canada.

The spectrum of requirements among the above mentioned countries is highly variable. In Japan and Canada DMF submissions in eCTD format are still not possible. In Europe and the USA, eCTD is considered the preferred submission format. Furthermore, the EDQM offers alternative ways to submit DMFs in electronic format (NeeS, or single pdf for the whole submission), while this is not foreseen for FDA and EMA.

Overall, a clear trend towards paper-free submissions, with preference for eCTD electronic format, is observed.

1.2 Requirements for the European Union

1.2.1 EDQM

General

A choice has to be made between an electronic or paper submission, excluding any combination of both. It must be noted that paper submissions are scanned before validation of the application which may lead to a delayed clock start.

Electronic submissions are strongly recommended.

Electronic submissions

Three formats are accepted:

- eCTD format (preferred format),
- NeeS format,
- single bookmarked PDF file.

Submission in eCTD format is recommended. The eCTD structure should be in accordance with the current ICH M2 EWG eCTD specification (see chapter 3).

Specific requirements for submissions to the EDQM include:

- the use of the EDQM template for QOS which has to be a pdf document,
- for eCTDs, the content of the envelope for a CEP application should be according to 'Guidance for Submission of Electronic Documentation for Applications for Certificates of Suitability (CEPs): Revised Procedures (PA/PH/CEP (09) 108)' [Reference 1].

Requirements for electronic files

Electronic files should be in accordance with the Guidance for Industry on Providing Regulatory Information in Electronic Format (see chapter 3 for further details).

Switch from a paper to an electronic submission

It is possible to switch to an e-submission at any time of the life-cycle of a CEP application (submission of a full module 3 is required). All subsequent data must then also be submitted in an electronic format.

EDQM guidance documents

There are two guidance documents:

- Guidance for Submission of Electronic Documentation [Reference 1]
  and
- Explanatory note [Reference 2]

1.2.2 Requirements for EU Countries

General

Some general information on electronic ASMF submission is available on websites. [Reference 3] and [Reference 4]

ASMFs submitted in eCTD need to be split into an applicant's part and a restricted part (see Guideline on Active Substance master File Procedure CHMP/QWP/227/02).
The applicant's part is expected to be located before the restricted part.

More information is available on the EMA website on electronic submissions, which also provides links to the National Agency e-Submission Guidance [Reference 3]

1.2.3 European Medicines Agency (EMA)

From 1 January 2010, eCTD is the only acceptable electronic format for all applications and all submission types in the context of the centralized procedure (e.g. new applications, variations, renewals). Any other electronic format, including NeeS, will be automatically rejected and the submission receipt will not be acknowledged. Additionally, if the eCTD submission results in an invalid Technical Validation the submission will not be accepted.

From 1 March 2014, all centralized eCTD filings must be made via the eSubmission Gateway or web client, no longer using CDs or DVDs.

1.3 Requirements for the United States of America

Information on the electronic submission of DMF can be found on the FDA website [Reference 5].

There is no requirement to submit DMFs in electronic format as paper will continue to be accepted. However, companies are encouraged to submit their DMFs in electronic form during the updating of their paper DMFs. Note that all applications to CDER, including DMFs, that are submitted in electronic format, MUST be in eCTD format, unless a waiver is granted.

NOTE: Before an eCTD submission is undertaken, the FDA requires a sample submission to be made in order to assess the technical aspects such as compatibility with the FDA system. More details can be found on the FDA website [Reference 6].

Companies may convert an existing DMF in paper format to eCTD format. In such cases DMF holders are advised to resubmit the entire DMF in CTD format as an amendment. If there are any changes in the technical content of the DMF as a result of the reformatting (e.g. addition of new information) the cover letter for the new electronic submission should specify what areas of technical information have been changed. Once the DMF holder has made an electronic submission every subsequent submission must be in electronic format.

Electronic signatures are accepted.

All electronic submissions must have a pre-assigned number. Pre-assignment of DMF Numbers will be granted only for electronic DMFs. If a paper DMF is being converted to electronic format, it is not necessary to request a pre-assigned number.

The request of pre-assigned Application number is described on FDA web page [Reference 7].

Note that eCTDs are seen as electronic records by FDA. This means that it needs to be compliant with 21 CFR part 11. The dossier is seen like all GMP-relevant electronic documentation, and all aspects of 21 CFR part 11 (e.g. electronic signatures, audit trails...) are applicable.

Related guidelines:

- Electronic Common Technical Document (eCTD) – [Reference 8]
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications – [Reference 9]

Helpdesk: esub@fda.hhs.gov

1.4 Requirements for Japan

At present, MHLW and KIKO do not accept eCTD submissions for DMFs.

For further information on specific submission requirements, it is advised to discuss with a Japanese agent.

1.5 Requirements for Canada

eCTD submissions are not possible for DMFs in Canada. Paper as well as single pdf submissions are accepted.

2 CHAPTER 2: OPTIONS & CONSIDERATIONS FOR API MANUFACTURERS TO HANDLE e-CTD REQUIREMENTS

2.1 Introduction

This chapter is intended to provide a decision pathway for API manufacturers in their first steps towards implementation of eCTD publishing and submission.

At the beginning of the decision process it is very important to make an evaluation of the current submission processes ("where are we") in comparison with the eCTD requirements ("where do we need to be"). (see Section 2.2).

The conclusions drawn from this analysis, together with a careful evaluation of the boundary conditions within the company (see Section 2.3) are the basis for the definition of the User Requirements Specifications (URS) (see Section 2.4). In the URS all the needs and boundaries of the expected processes are described and this information is used to find the optimal solution (see Section 2.5). Three possible solutions are described in detail, with their related advantages and disadvantages: in-house software (see Section 2.5.1), Software as a Service (SaaS) (see Section 2.5.2), and outsourcing (see Section 2.5.3). The last step of the process is the implementation of the chosen solution.

Please note that the overall chapter focuses on the initial set-up for eCTD submission. However, submission management of products through-out their life cycle is a key aspect and needs to be considered for all options from the very beginning.

2.2 Evaluation of current submission processes & tools

The decision pathway towards the optimal solution for eCTD publishing and submission starts with a careful analysis of the current processes and tools with respect to the requirements of eCTD publishing and submission. The important questions to consider are:

- What is the current status?
- What are the gaps with respect to eCTD publishing and submission?

In detail, the items to be evaluated are:

- Document creation and lifecycle process (who writes the document, is there a review/approval process, how is the document lifecycle managed, are module 1 documents included in this process etc.?)
- Document creation tools (is there a template, is the granularity and the document characteristics compliant with eCTD specifications etc.?)
- Publishing and submission process (who compiles the dossiers, who sends the dossiers to customers and authorities, what archiving system is in place etc. ?)

2.3 Boundaries

For each of the items described in 2.2 it is important to define the boundary conditions:

What can or cannot be changed (e.g. resources)? Do we want to change anything else? The impact of any change needs to be evaluated.

Example of “Boundary questions”:

- IT support available/willing to help?
- Dedicated resources in Regulatory Affairs and IT?
- Support of any other departments that can interact in dossiers preparation? In system implementation (Quality Assurance, Validation etc.)?

2.4 User Requirement Specification (URS)

The URS is a document that describes, on a non-technical level, the requirement for the new system. It contains the individual needs and preferences of a company, i.e. the requirements resulting from the initial process analysis and boundary definition and reflects the requirements from all stake-holders, e.g. regulatory affairs, IT, QA, authors of documents. In summary, this document is the basis for the later selection of the optimal solution and the related vendor /system. The system is also tested against these requirements during qualification.

Examples of topics to address during user requirement setting (beyond eCTD requirements) are:

- How is the organization of the regulatory group in the company? (i.e. global, regional or local)
- How many submissions take place / are expected per year? In which countries?
- Are non-eCTD submissions (electronic or paper) still needed? How can they be created out of the system?
- Is it necessary to create non-CTD structures for dossiers? How can such a structure be built up?
- How to handle submissions in more than one country?

It has to be considered whether a consultant should help with the creation of this URS document. Especially for the generation of the new processes the experience of a consultant can be helpful.

The URS is part of the official validation documentation according to GAMP and should be established for any new system. For further information please refer to GAMP 5. ‘GAMP® 5 : A Risk-Based Approach to Compliant GxP Computerized Systems’ can be bought through the following link : http://www.ispe.org/gamp-5

2.5 Selection of solution

Once the URS has been finalised, the most suitable solution has to be found. For this analysis the URS requirements should be classified in some way, e.g. “crucial” and “nice to have”.

The three possible solutions (In-house Software, Software as a Service and Outsourcing) are described in detail in the following sections. Table 1 compares the most relevant characteristics of the 3 solutions.

Table 1: Comparison of the 3 solutions

Item	**In-House software**	**Software as a Service**	**Outsourcing**
Freedom of configuration	high	limited	No
Responsibility for update and Maintenance	high	no	No
IT support in-house needed	yes	no	No
Link to other IT systems in-house possible	yes	no	No
Initial costs	high	low	No
Ongoing costs	in-house	yes	Yes
Lead time	long	medium	short
Scalability	Depends on set-up	easy	Easy
Nneed of resources and competence for use of eCTD software	yes	yes	No
confidentiality / data security issues	no	yes	Yes

2.5.1 In-house software

Implementing an eCTD software system in-house gives the highest degree of freedom. The software can be designed to meet the company's specific requirements. Implementing an in-house system, however, will also require the highest level of responsibility.

Considerations that will help to decide if the in-house approach is suitable and how to plan, implement, and maintain the in-house system is detailed in Table 2.

Table 2: Running an eCTD software system in-house: advantages and disadvantages

Advantages	Disadvantages
Full freedom for configuration	High initial costs for setting up the system
Free choice of hardware and software components	Relatively long lead time needed to set up the system
The software is part of the company-owned software and fits into the IT concept of the company	Full responsibility for update and maintenance
Everything stays in house (no data-transfer via internet / confidentiality etc.)	Personnel for technical set-up and maintenance must be available.
Link-up to other IT-systems possible (e.g. SAP)	
Maintenance costs stay in-house	
On-going costs are lower compared to the host software or outsourcing options	

Possible vendors should receive the URS and are requested to provide feedback indicating the points of the URS that can be fulfilled:

- by their standard product without modification
- by configuration of their standard product
- by customisation of their standard product
- not at all.

An initial presentation and demonstration should be provided by the potential vendor in front of users of the system (i.e. all users or a representative selection and key players from the IT department). It should focus on their standard product. The main aspects of the new software should be discussed and reviewed. Vendors that do not fulfil the crucial requirements can be removed from the selection process. In a second round the vendors should sketch out solutions for all important requirements - establishing a vendor score card can help in the decision making.

Main criteria for the selection can be:

- Are the requirements met?
  - What are the gaps?
  - How important are the gaps? → What does this mean for the defined processes?
- What are the costs for
  - Licenses?
  - Implementation of the software?
  - Migration of legacy documents and dossiers?
  - Maintenance?
- What software is used?
  - Compatibility with the systems of the regulatory agencies and other service providers.
  - User friendliness of the software and coverage of needs of the user/customer.
  - What configuration options are offered?
  - Validation and CFR 21 Part 11 (Electronic Records - including Electronic Signatures,(US) and EU GMP Guide Annex 11) compliance and maintenance of the computerized system(s), change control management.
- What hardware is needed?
  - How many servers are necessary?
  - What server capacity is needed, also taking life cycle management into account?
  - What are the operating systems?
  - Can a virtual environment being used instead of dedicated servers?
- Work share within regulatory.
  - Who will use the system (central unit / everyone contributing to regulatory documents)?
  - How will the users access the system
    - Local installation
    - Client / server application
    - Remote access (e.g. via Citrix)
- Soft factors are also very important.
  - Who will be the contact person(s) for the project at the vendor?
  - Can a good cooperation be expected with contact person(s)
  - There will be cooperation with the vendor for the complete lifetime of the system. Therefore a good contact with this company is important.
- Reference list of the vendor.
  - Who are the customers?
  - Is there contact to authorities?
  - What is the market position of the vendor?

When deciding if an in-house software system is suitable, the complete life-cycle of the system should be considered such as:

- Building up the system and migrating legacy data into this system, as appropriate.
- Training of users and roll-out into the organisation (production phase).
- Maintenance of the system needs to be planned (training and SOPs for technical staff etc.)
- An update-strategy must be in place (i.e. retirement of the old system and replacement by a new one).

2.5.2 Host system option / Software as a Service (SaaS)

In the Host Software Option, also called “Software as a Service” (SaaS) or “rental approach”, the service provider provides the IT infrastructure for the creation of eCTD dossiers whereas the customer controls the submission activities and prepares the submission.

The information provided in this section is based on publically available information and a common sense approach. This is because the eCTD Task Force members do not yet have their own experience with this option.

In the SaaS model the installation, validation and maintenance of the eCTD system (and DMS system if both shall be hosted) are under the responsibility of the provider. The customer rents the usage of the infrastructure/software.

Advantages and disadvantages of using the Software as a Service option are described in Table 3 .

Table 3: Host system option: advantages and disadvantages

Advantages	Disadvantages
Speed: time from the decision to a pilot eCTD is often shorter compared to the in-house software solution	Dependency on an external partner which increases if also the DMS shall be hosted
Lower cost for initial implementation as there is no or a smaller initial investment (e.g. initial set-up, user and software licenses, maintenance)	Data transfer via internet (confidentiality, upload / down load capacity)
Scalable: ability to scale as business needs change	Data hosted at an external company (confidentiality)
No on-going system maintenance	Limited freedom for software configuration
	On-going costs for renting the system/service

The SaaS option requires minimal IT support (compared to the in-house software solution) on the customer’s side whereas the resources and competences for the eCTD software (and DMS as applicable) need to be built up and maintained. The “eCTD builder & publisher” needs to have a specific technical qualification to efficiently work with the eCTD software. This requires respective training but also regular use of the system and practice with it. The training should be completed before using the system.

Respective SOPs, user manuals, training materials need to be available. This should be supported by the service provider.

As with any other service provider, the potential partner for the host system should be qualified. Additionally to that listed in section 2.5, the following areas (not exhaustive) should be evaluated as part of the selection and qualification process:

- Management of confidential data (e.g. by service provider / between different customers) by the service provider
- Data security at the service provider (back-up/restore disaster recovery procedures) and setting-up of secure interaction with the customer (electronic data exchange)
- Measures for business continuity
- System availability
- System performance
  - speed and continuity of internet connection (e.g. for the upload, download of files, data)
  - download and upload capacities
- Quality management system of the service provider

The qualification process should include an audit of the potential service provider.

2.5.3 Outsourcing option

The option with the lowest impact on processes and systems in a company is outsourcing. There are various different extents of outsourcing. Common to all is that the external partner will provide the necessary infrastructure / software as well as the personnel to prepare the eCTD.

The considerations in this chapter mainly focus on the aspect of outsourcing the eCTD submission building / publishing part without the actual submission part. In addition to the outsourcing extent discussed, intermediate levels of outsourcing can be considered, e.g. creation of eCTD ready documents (new documents, legacy documents).

Table 4: Outsourcing option: advantages and disadvantages

Advantages	Disadvantages
Speed: time from the decision to a pilot eCTD is very short	Dependency on an external partner for each project and throughout the life cycle of a submission
No initial investment and no reoccurring costs for system maintenance and technical support	On-going costs for each service during the whole lifecycle of a product/submission (initial submission(s), variations etc.)
No direct costs for software, licenses, hardware, system validation and maintenance, training	Data transfer (confidentiality, upload / down load capacity)
No need to establish, maintain technical knowledge in building and publishing eCTDs, no need for respective in-house resources (eCTD builder/publisher)	Data hosted at an external company (confidentiality)
Scalable: ability to scale as business needs change	
Can also substantially-reduce risk of failed initial submissions	

There are 4 main scenarios that can drive the decision for outsourcing:

- there is no in-house software available to build / publish eCTDs or
- the in-house capacities are too little
- to gain experience for the creation of eCTD ready documents and eCTD submissions in-house
- the number of eCTD submissions is too small, seldom use of the system

On the other hand, the interface to the service provider is a key element in the process. Several questions need to be answered:

- Format of the data to be delivered
  - word / pdf / rft files with some additional attributes
  - “as is” files
  - eCTD ready files
- How will data be exchanged for building the eCTD and afterwards?
- Project management
  - A key element is to align the time point of availability of the different documents for the filing and the resources at the outsourcing partner, e.g. by using a shared and continuously updated document inventory
  - Definition of role, responsibilities and tasks of the project team members of both partners

- Management of the lifecycle of a submission
  - Process as part of answering deficiency letters
  - Variations
  - Submissions according to the requirements of different authorities

Cooperation with the Outsourcing Partner:

1. eCTD Project set-up
   - Define project team members (internal & outsourcing partner), roles responsibilities, milestones & timelines
   - Develop project plan: As time lines are always crucial in a submission process, and an additional/external party is involved, a mutually agreed project plan is vital
   - Set up of a secure internet connection (VPN) for smooth transfer of documents
2. Inventory of documents
   - This inventory can be used by both parties as a tracking and monitoring tool for establishing the completeness of documents (availability of document, eCTD readiness of document) and missing elements

As with any other service provider, the potential outsourcing partner for publishing should be qualified. Additionally to what is listed in section 2.5, the following areas should be evaluated as part of this process (note that this list is not exhaustive) :

- eCTD building and publishing competence and experience of the service provider (technical and regarding the requirements of the different authorities)
- Capacities
- Validation and maintenance of the computerised system
- Change management
- Management of confidential data, data security at the service provider and interaction with the customer (electronic data exchange)
- Quality management system of the service provider

2.6 Implementation

Once the decision for the best solution has been made, the internal processes should be reviewed and adapted where appropriate in order to best fit to the new situation of eCTD publishing. The extent of the review and the necessary improvements might be smaller for an outsourcing solution than in a host or in-house eCTD solution. However the opportunity to align the processes to the new situation should not be missed.

There are other decisions that are not process related but influence the implementation of the eCTD system:

- Validation of the system and validation approach
- Cooperation within regulatory affairs and to other groups/departments influences the processes. Work-sharing within regulatory touches the tasks of a publishing group and their interface to the colleagues who write documents and compile dossiers.
- A very important decision is the decision for or against a document management system.

2.6.1 Document management system (DMS)

Most eCTD submission tools support the use of documents out of a DMS as well as the documents out of the file system. Here are some points of consideration for and against a DMS.

A DMS is another software-component that has to be chosen, bought, designed, configured, validated and maintained. As well as the financial and technical aspects training to use the DMS is also required.

However, there are a couple of advantages in using a DMS: The documents are controlled in a more defined way.

Each document in the DMS consists of :

- the Content (as Word- and / or pdf-file)
- the Attributes
- the Access Control Lists.

The *Content* is the document e.g. the Word document containing the information that has to be sent to authorities.

The *Attributes* are used to facilitate searching for documents. In addition they can be used as part of a document overlay (document header and footer).

The *Access Control Lists* make the document available for different groups of users, with different rights at different stages of the life-cycle (see below).

When designing a DMS, life-cycles for documents can be implemented. A life-cycle controls the different states of the document and how it will get from one status into the next. The release of documents can be coupled with an approval which may include an electronic signature.

Documents are normally submitted as pdf-files to authorities. A DMS may be able to automatically create pdf-files out of editable source files at a certain life-cycle step.

When using a document management system it is possible to store documents in a predefined folder structure where they cannot be moved. This facilitates re-use of documents by different users.

As this is not an exhaustive list, we refer to literature for more information about document management systems.

2.6.2 Creation of eCTD compliant documents

For any new submissions it should be considered to develop documents as close as possible as eCTD ready documents (right first time, avoidance of later extensive reformatting). Areas to be considered are:

- use of templates for authoring eCTD ready documents (see chapter 3: granularity, file formats)
- use of a file system or DMS to manage the files
- internal roles & responsibilities for the various steps of the process
  - who is authoring documents, quality control, approval, filing and interfaces
  - how is version control of documents and submissions established
  - archiving

In case eCTD ready documents are created in-house, respective templates should be established and implemented. The process of developing and managing eCTD-ready documents needs be established (e.g. responsibilities and interfaces different departments) and defined in respective procedures.

2.6.3 Service agreement (Host System of Outsourcing Options)

As a matter of fact, the availability of a confidentiality agreement between the service provider and the customer is a must for any collaboration as well as a service agreement. The service agreement should clearly define the responsibility of both parties and the agreed service levels, e.g. minimum system performance metrics.

2.6.4 Users and Training

The users of an eCTD software are normally in the regulatory department. With the introduction of a new document-management and / or submission system it needs to be defined who should have access to the system and at what level. Different types and extent of trainings will be needed for the different levels.

Training concept, training material, and roll-out-plan should be available and training should be completed before the go-life of the system.

2.6.5 SOPs

Technical and user-SOPs will be necessary for the valid operation of the software. They should be in place before the system 'goes live'.
In addition to the SOPs directly associated with the use of the system, the potentially new internal process e.g. activities, roles & responsibilities (i.e. authoring eCTD ready documents, submission and maintenance of a dossier) should be reflected in written procedures.

Also, the process of using an external partner for the eCTD compilation and publishing should be reflected in respective SOPs.

2.6.6 Document Migration

See chapter 3.3 "Migration of data into the new eCTD system".

3 CHAPTER 3: PREPARATION OF e-CTD READY DOCUMENT AND DOSSIERS

It is important that eCTD ready documents are prepared by authoring them in eCTD compliant templates. If this is not undertaken, a large amount of the "publishing time" is spent in document reformatting. Guidance on the preparation of eCTD ready documents is provided below.

3.1 File Organisation for the eCTD (Granularity)

Reference

ICH Topic M 4 Common Technical Document for the Registration of Pharmaceuticals for Human Use [Reference 10].

Table 5 and Table 6 describe the levels in the eCTD hierarchy at which files should be placed and whether single or multiple documents are appropriate at each point. The tables describe Modules 2 and 3 with respect to the drug substance.

For creation and maintenance of the files, the storage location does not have to be considered. The hierarchy structure will be applied during the compilation of the dossier.

Table 5: Module 2

<table>
<tr><td rowspan="8">Module 2</td><td rowspan="8">2.3 [1]</td><td>Introduction</td><td></td></tr>
<tr><td rowspan="7">2.3.S [2]</td><td>2.3.S.1</td></tr>
<tr><td>2.3.S.2</td></tr>
<tr><td>2.3.S.3</td></tr>
<tr><td>2.3.S.4</td></tr>
<tr><td>2.3.S.5</td></tr>
<tr><td>2.3.S.6</td></tr>
<tr><td>2.3.S.7</td></tr>
</table>

KEY
Documents rolled up to this level are not considered appropriate
One document may be submitted at this level

Note 1: The options for granularity for the Quality Overall Summary (QOS) are provided in order to accommodate different levels of complexity of products. The applicant can chose the level at which the QOS is managed.

Note 2: One document should be submitted for each drug substance.

Table 6 : Module 3

<table>
<tr><td rowspan="20">Module 3 [1]</td><td rowspan="20">3.2</td><td rowspan="20">3.2.S [2]</td><td rowspan="3">3.2.S.1</td><td>3.2.S.1.1</td></tr>
<tr><td>3.2.S.1.2</td></tr>
<tr><td>3.2.S.1.3</td></tr>
<tr><td rowspan="6">3.2.S.2</td><td>3.2.S.2.1</td></tr>
<tr><td>3.2.S.2.2</td></tr>
<tr><td>3.2.S.2.3</td></tr>
<tr><td>3.2.S.2.4</td></tr>
<tr><td>3.2.S.2.5</td></tr>
<tr><td>3.2.S.2.6</td></tr>
<tr><td rowspan="2">3.2.S.3</td><td>3.2.S.3.1</td></tr>
<tr><td>3.2.S.3.2</td></tr>
<tr><td rowspan="5">3.2.S.4</td><td>3.2.S.4.1</td></tr>
<tr><td>3.2.S.4.2</td></tr>
<tr><td>3.2.S.4.3</td></tr>
<tr><td>3.2.S.4.4</td></tr>
<tr><td>3.2.S.4.5</td></tr>
<tr><td>3.2.S.5</td><td></td></tr>
<tr><td>3.2.S.6</td><td></td></tr>
<tr><td rowspan="3">3.2.S.7</td><td>3.2.S.7.1</td></tr>
<tr><td>3.2.S.7.2</td></tr>
<tr><td>3.2.S.7.3</td></tr>
<tr><td colspan="5">KEY</td></tr>
<tr><td colspan="5">Documents rolled up to this level are not considered appropriate</td></tr>
<tr><td colspan="5">One or multiple documents can be submitted at this level</td></tr>
</table>

Note 1: In choosing the level of granularity for this Module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete files should be provided in the eCTD.

Note 2: For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

The files have to be created according to the granularity described above. They have to be linked into the CTD structure that is presented in the eCTD submission tool.

3.2 Specification for Submission Formats

3.2.1 Introduction

This chapter is based upon ICH M2 EWG Electronic Common Technical Document Specification [Reference 11] and focuses specifically on the Active Substance Master File requirements

3.2.2 Specification for Submission Formats

In general, documents that are provided in the different modules should be formatted as defined by the ICH Common Technical Document. Here it is described how files should be constructed for inclusion in the eCTD and examples of formats that are commonly used in electronic submissions are provided. It should also be noted that other formats can be used according to regional guidance and/or acceptance.

The different key items to be considered when creating an eCTD compliant document are summarised in Table 7. This table is based on requirements of ICH M2 EWG document (ICH eCTD specification) [Reference 11].
A published dossier should be checked for viruses before submission. The recommended way of transporting submissions is secure data exchange over the Internet. If this is not possible, submissions should continue to be physically transported by courier or registered mail. In this case, electronic media needs to be labelled appropriately.

Table 7: Key requirements for the creation of eCTD compliant documents

Document format :	Pdf version 1.4 or (up to) 1.7 optimized for fast web view
Source of electronic documents	Documents should be generated from electronic source documents. Scanned documents are discouraged and accepted only in exceptional cases
File naming	File names are limited in length to 64 characters. They should contain only lower case characters, no special characters except hyphens should be used.
Fonts	Recommended fonts are Times New Roman, Arial, Courier New. All additional fonts should be embedded.
Font size	Narrative text: e.g. TNR 12 points. Tables: e.g. TNR 9-10 points, smaller character size is discouraged
Font colour	Black recommended, blue for hyperlinks
Page orientation	Only portrait orientation is accepted for eCTD documents. If there is a need to present the content in landscape orientation, the page should still be oriented as portrait.
Paper size and margins	Print area should fit on both A4 and letter format
Headers and footers	All pages of a document should include a unique header or footer briefly identifying its subject matter (e.g. study/report identifier, batch number). It does not necessarily have to contain the CTD section identifier or other metadata.
hypertext linking and bookmarks	Cross-references (intra- and inter-documents) can be supported through the use of hyperlinks. Hyperlinks should be used advisedly as they may cause problems with follow-up submissions.*
page numbering	Only the internal page numbers of the document are expected (1-n). No additional page/volume numbers running across documents are expected. The page numbers for the electronic document and the PDF file should be the same
dialog box	The open dialog box defines the document view when the pdf file is opened. The initial view of PDF files should be set as Bookmarks and Page, or Page only if there are no bookmarks.
Security	No security settings or password protection for PDF files should be included. Printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields should be allowed.
electronic signatures	Although electronic signatures are currently accepted in the EU and US, we recommend to consult the Website of NCAs in case of National submission

* The EMA/43526/2010 V.1.0 Practical Guidelines on the use of the eCTD format for ASMFs [Reference 12] (page 5) states that the use of hyperlinks between documents in Module 3 is not recommended as problems may arise due to file-naming recommendations and life cycle management.

3.2.3 Guidance on Text Searchable Documents

Reference

TIGes Harmonised Guidance for e-CTD Submissions in the EU – annex 2 [Reference 13]

3.2.3.1 General

All submissions must contain the maximum amount of text searchable content. Documents with searchable text will aid the assessor, or any other user, in searching for specific terms and also aid in the copying and pasting information into other documents such as an assessment report. Nevertheless, not all documents need to be text searchable.

3.2.3.2 Creating Text Searchable Files

PDF files with searchable text can be created by all PDF tools from a source file in a text format (e.g. MS Word, SAS, MS Powerpoint, Rich Text Files, etc.). When created in this way, the file will usually be the smallest in size (measured in kilobytes or megabytes) that it can be.

If the document is in paper, then scanning to PDF and using an Optical Character Recognition (OCR) routine is the only way to create searchable text. PDF files created in this way tend to be much larger in size for the same number of pages and the quality of the text that is created will be poorer. For these reasons, it is recommended to use scanning/OCR only as a last resort.

3.2.3.3 Documents that must always be text searchable

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then they **must be** OCR'd.)

- Key administrative documents in Module 1 including, the cover letter, application form, product information documents
- Any document in Module 2 of the MAA (QOS).
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 of the MAA
- Any English translation of a document originally written in a foreign language (see also below)

3.2.3.4 Documents that do not need to be text searchable (relevant for the API part)

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then there is no need for OCR.)

- Any original GMP certificate
- Any original certificate of analysis
- Any manufacturer's licenses
- Any certificate of suitability
- Any Manufacturing Authorization

- Any document written in a foreign language where a translation is provided in English (however, the translation should be text searchable, see above)
- 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).
- Any page with a signature that does not contain other information key to the understanding of the submission
- Applicants should consider providing signatures on separate pages from key text in reports, overviews, etc.

3.2.4 Regional Requirements: Module 1 requirements for eCTD submissions

Module 1 of the eCTD contains administrative information specific to each region, e.g. application forms. The content and format of this module are specified by the relevant regulatory authorities. This section of the How to Do document provides an overview of the relevant documents and necessary structure in Module 1 related to APIs in some key regions.

3.2.4.1 Module 1 documents for EMA and EDQM

With respect to the ASMF / DMF, the information that has to be provided in Module 1 relating to the authority and the initial submission is listed in Table . Where a document is required, the respective section is indicated in brackets. For information on revisions and renewals please refer to the referenced documents.

Table 8 : Module 1 requirements

Document	EMA*	EDQM
Cover letter	X (1.0)	X (1.0)
Letter of Access	X (1.0)	
Application Form	X (1.2)	X (1.2)
Information Quality Expert	X (1.4)	X (1.4)

* National authorities may have additional module 1 requirements.

References:

EMA:

- EMA/43526/2010 V.1.0 Practical Guidelines on the use of the eCTD format for ASMFs [Reference 12]

EDQM:

- Guidance for submission of electronic applications for CEPs: Revised procedures - PA/PH/CEP (09) 108, 1R [Reference 2]

3.2.4.2 Module 1 documents for FDA

The document provided by FDA for guidance in an eCTD submission does not distinguish between the drug substance and the drug product. As a result it contains the complete CTD Headings and Hierarchy.

FDA follows the granularity outlined in M4 - ICH Common Technical Document and in M2 - ICH Electronic Common Technical Document Specification [Reference 10] and [Reference 11]

Table 9 details what information should be contained in Module 1

Table 9 : Module 1 information

Section	Document
1.11	Information amendement
1.11.1	Quality information amendement
1.13	Annual report
1.2	Cover Letter and Statement of Committment
1.3 1.3.1 1.3.1.1 1.3.1.2	Administrative Information Contact/sponsor/Applicant information Change of address or corporate name e.g. to supply addresses of DMF holder and manufacturing and testing facilities Change in contact/agent e.g. to supply name and address of contact persons and/or agents, including Agent Appointment Letter
1.4.1 1.4.2 1.4.3	Letter of Authorization (LOA) Submission by the owner of information, giving authorization for the information to be used by another Statement of Right of Reference Submission by recipient of a Letter of Authorization with a copy of the LOA and statement of right of reference. Submitted in a DMF only when another DMF is referenced. List of authorized persons to incorporate by reference List should be submitted in DMF annual reports.
1.12.14	Environmental Analysis

FDA mandates the submission of a sample eCTD for evaluation. The FDA will process the sample submission to ensure that it conforms to FDA and ICH guidance and specifications. These tests include, but are not limited to, validation, verification of file checksums, verification of the presence of the modified file and identification of missing files.

This sample eCTD submission will not be reviewed by an assessor during this initial test. The FDA will, however, provide the participant with a report highlighting the errors found during the initial processing of the sample eCTD submission. The error identified should be corrected and the corrected sample should then be re-submitted with the same sequence number.

After the successful completion of these steps, the submissions should be technically ready to be officially submitted to the Agency. This testing phase does not involve any review of the content of the submission and is intended to only resolve technical issues.

3.2.4.3 Further reading

eCTD electronic Submissions

[Reference 13]

electronic Submissions (FDA)

[Reference 14] and [Reference 15]

Portable Document Format Specifications

[Reference 16]

3.3 Migration of data into the new eCTD system

An eCTD dossier consists of a number of documents that are linked into the specific eCTD tree. The eCTD specification and granularity annex (see chapter 3.1) lists the different sections of ASMF together with the document(s) that are expected in each section.

This chapter describes the criteria for eCTD ready documents. If legacy documents should be used in eCTD submissions, they also have to comply with these standards. This section describes some considerations for the migration of legacy documents into eCTD ready documents.

3.3.1 Migration of documents

The easiest way for the user is an automatic migration without any interaction. In most cases automatic migration is possible but the development of tools is time consuming and costly with respect to setting up a specification for each job and testing of the resulting program.

Therefore, for each job a careful decision should be made as to whether this task should be done automatically (a job that has only to be started once for the productive migration), semi-automatically with the help of some macros (e.g. for the migration of specific documents) or completely manually. If for example the document migration is done completely automatically, all the legacy documents are available for eCTD submissions right after the migration program has finished. The program may run for a couple of hours or even longer but after this initial action the complete task is finished. Manual or semi-automatic migration can either be done by a migration team right after go-live of the eCTD system, or the documents and dossiers are migrated when they are needed. Therefore extra time is required at the time the document or dossier is requested.

Documents can either be maintained within a DMS or within a file system (folder structure). If the legacy documents are hosted in a DMS, it has to be decided whether the existing DMS can also be used for the eCTD system or a new DMS has to be designed to manage eCTD documents. When working with files in a file system the eCTD ready document can either stay in a file system or be migrated into a new DMS.

The main difference of a DMS compared to a file system is that a document in a file system consists only of the content of the document itself. Whereas, a document in a DMS is built up on the content plus a set of attributes that can be used to specify the document and add additional information to the document. Those attributes can usually be used as basis for searching in a DMS.

Paragraph 3.3.1.1 is connected with content related issues that have to be considered in each case. The paragraph 3.3.1.2 holds attribute related issues that are only necessary when dealing with a DMS.

3.3.1.1 Content related issues

3.3.1.1.1 Document granularity

Since legacy documents do not necessarily have the right granularity it may be necessary to split or merge documents. Document granularity is described in Chapter 3.1 (File organization of the eCTD).

Splitting documents is very time consuming. It should be considered, if an automatic or semi-automatic splitting is advantageous.

Merging documents is easier. Nevertheless an automatic or semi-automatic way is worth consideration.

3.3.1.1.2 Re-use of documents

One of the most prominent advantages of CTD granular documents is the possibility to re-use documents. An eCTD ready Submission Management System (SMS) should be able to report the occurrences of a document in different dossiers

For example, the specification of a specific solvent needs only be maintained once. If the specification of this solvent changes the impact of the change can be easily evaluated with the help of the above mentioned function. This can help to keep compliance of the dossiers. It is therefore recommended to maintain only 1 document for the above mentioned specification. If the content of all duplicate documents is not the same, it might be necessary to consolidate the content of the existing documents.

3.3.1.1.3 Adaptation of formats

When designing the SMS, the page format can be completely redefined. If there are different legacy systems, text files can have different header and footer areas and even different dimensions (A4, letter, etc.). Migrating all systems onto 1 new system will result in a redefinition of the header, footer and / or page dimensions. It may therefore be necessary to copy the content of a file into a new template. This task can be done with the help of a macro for a semi-automatic migration or can be part of a complete automatic migration program.

For more information see chapter 3.3.1.2.

3.3.1.1.4 Change of document type

The greatest impact for a document is the change of the document type (for example a spread-sheet in the legacy system is to be changed into a text-document). As with the other tasks discussed in this section, it has to be considered whether manual migration of these documents would be better.

3.3.1.2 Attribute related issues

Attributes are only relevant when the eCTD system uses a DMS for document maintenance. The easiest case occurs when the set of attributes for the documents in the legacy DMS and the new DMS are identical. In all other cases attributes have to be added, modified or deleted.

3.3.1.2.1 Header and Footer

Headers and footers for documents can hold information about the document and its position in the dossier. The header of a document can, for example, state:

- the name of the API
- the CTD section of the document
- the title of the document according to eCTD specification (see Section 3.1)

The footer may state information such as the page number and the publishing date. If the documents have document numbers they can also be mentioned in the footer.

Most of the above mentioned information can be provided by the SMS and can be put on the document by an overlay during the publishing process. This option could be useful when documents should be re-used for different DMFs and the name of the API is mentioned in the header. For that reason, document content shall be as neutral as possible without reference to any other submission i.e. country or submission number.

Information in the header must be provided by the SMS since the name of the API will be different for different DMFs. It is, for example only necessary to hold 1 manufacturer‘s document for a specific production site. Then neither the name of the API nor the document title can be part of the document since different DMFs are for different APIs By consequence, the content of the document and the header/footer are separated..

3.3.1.2.2 Migration from an already existing legacy DMS

The starting point for the migration from an attribute-related view is a comparison of the attributes:

- What attributes are used in the existing system?
- What attributes are needed to compile eCTD DMFs?
- Is it possible to rededicate attributes and/or to add new attributes in order to get a set of attributes that can be used for eCTDs?

The result of these considerations will be:

- The actual DMS can be used without modifications to host eCTD documents.
- Some modifications and/or an upgrade of the DMS are necessary.
- A new system should be implemented.

If the current system can be used the legacy documents have to be migrated into eCTD ready documents. If the granularity of the documents is correct, it is only necessary to update the attribute sets of the documents. This can either be done by the manual edition of each attribute set. The other option is to export all attribute sets with or without the documents, modify the attributes outside the DMS and re-import the attributes. If only the attributes were exported, it has to be ensured that the attributes connect with the right documents. The modification of the attributes can be done manually or with the help of exchange tables.

If the granularity of the documents is not correct, it is recommend to export the documents together with the attributes. The documents then have to be split up and the attributes have to be adapted. The new documents, together with the attribute-sets, have to be imported into the DMS again.

3.3.1.2.3 Migration from file system to DMS

When migrating documents from a file system into a DMS the attribute set has to be created and the (granular) documents have to be imported into the DMS. This can again either be done manually or with the help of programs.

Manual migration

For manual migration, the files have to be split if necessary and the new (granular) files have to be imported into the DMS. During importation the attributes will be maintained.

Migration with the help of programs

If all documents that represent the legacy document have to be imported in one step, the attributes of the documents must be adapted before the import starts.

The import of a set of documents has to be done with the help of a table. This table has to hold the attributes and the file names and storage locations (paths) of the documents, so that a set of attributes can be related to a document.

Such a table can be filled with the help of programs during the migration of the legacy documents into eCTD compliant document.

3.3.1.2.4 Migration within a file system

When the legacy documents and the eCTD ready documents are hosted in files systems no attribute related issues will occur.

3.3.1.3 Import of paper documents

According to ICH-eCTD specification[1] it is possible to scan paper documents but it is not recommended.

For more details see chapter 3.2.

3.3.2 Dossier migration into a SMS

Once eCTD ready document are available an eCTD dossier can be prepared.

An eCTD dossier is built up of the XML-backbone that reflects the CTD structure. Each document is linked into this structure at its respective CTD-section.

A SMS should enable a user to create the eCTD dossier and to link the documents into the dossier. It can therefore be considered that the most difficult part of dossier creation is finding the documents that have to be linked into the specific nodes of the structure. It is recommended to try the creation of dossier during the vendor presentations with a set of sample documents. This will help to estimate the time needed to create a new dossier.

Furthermore, this will give you an indication of the time necessary for the migration of a dossier. If the number of dossiers is limited this is considered the best way.

An automatic migration requires a very thorough analysis of the legacy dossiers. In addition the connection between the legacy documents and the new eCTD ready documents must be established, so that the migration program is able to link the correct documents into the new structure. If more than one different type of legacy dossiers are affected then considerations for each system should be undertaken separately. Since both requirements are not easy to fulfil, the number of dossiers to be migrated will have to be large to justify an automatic migration.

See [Reference 17]

[1] ICH M2 EWG, section 7-3 [Reference 11]

ANNEX 1: GLOSSARY /Abbreviations

Term	Definition
API	Active Pharmaceutical Ingredient
Architecture	A general term for the design and construction of computer systems, including technical infrastructure,information (data), and applications.
ASCII	American Standard Code for Information Interchange. A specification for representing text as computerreadableinformation.
ASMF	Active Substance Master File
Attribute	Attributes are used to describe the content or context of a document (e.g. file name, the name of a related substance etc.)
Bookmark	A bookmark is a type of link with representative that links to a different view or page in a document.
Browser	A program that allows the user to read hypertext, to view contents of Web pages, and to navigate from onepage to another (e.g., Mozilla Firefox, Microsoft Internet Explorer.)
CDER	FDA-Group: Center of Drug Evaluation and Research
CEP	European procedure for a certificate of suitability of monographs of the European Parmacopoiea
CFR 21 part 11	Code of Federal Regulations - 21 - part 11 on electonic records and signatures
Citrix-server	Server with a desktop virtualisation software from Citrix Systems Inc. Installed.
CTD (Common Technical Document)	A harmonized format for a regulatory dossier that is considered acceptable in Japan, Europe, the United States and Canada.
CoS	Certificate of Suitability (see also CEP)
CFR	Code of Federal Regulations
Directory (see also Folder)	The operating system method of organizing and providing access to individual files. Also called a folder.
DMF	Drug Master File
DMS	Document Management System
DTD	Document Type Definition. A hierarchical organization or representation of the information contents of a document utilized by SGML or XML
eCTD	The electronic format of the ICH Common Technical Document (as defined by ICH)
EDQM	European Directorate for the Quality of Medicines
EMA	European Medical Agency
EMEA	European Medicines Evaluation Agency (predecessor of EMA)
Envelope	Part of the Module 1 specification. EU Modul 1 Specification defines the envelope as a root element that provides meta-data (attributes) for the submission.
ESTRI	Electronic Standards for the Transfer of Regulatory Information.
EWG	Expert Working Group (EMA)
FDA	Food and Drug Administration

Term	Definition
Folder (see also Directory)	The operating system method of organizing and providing access to individual files. Also called a directory.
GAMP	Good Automation Manufacturing Practices (Organization issuing the GAMP guide)
Granularity	Description of number of documents allowed for each CTD (sub-) chapter (see ICH guideline on "ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE M4")
HTML	Hypertext Markup Language. Commonly used to format Web pages.
Hypertext	A system that enables links to be established between specific words or figures in a document to other text, tables or image allowing quick access to the linked items (such as on the World Wide Web).
Hypertext linking	A system that enables links to be established between specific words or figures in a document to other text, tables or image allowing quick access to the linked items (such as on the World Wide Web).
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
Infrastructure	The basic support services for computing; the hardware, operating system, and network on which applications and data are stored and on which the database management systems run.
IT	Information Technology
KIKO	Japan's Drug Organisation
Leaf	The eCTD DTD XML element that describes the content to be provided. The leaf consists of a file and the meta-data associated with that file. Such files are placed in a directory structure that is similar to branches of a tree.
Legacy document	A document from a former system (document management system or file system)
LOA	Letter of Access / Letter of Authorization
Logical Document	One or more CTD table of contents sections that together contain the minimum amount of information to be exchanged. Ideally, this is a single physical file.
M2	Multidisciplinary Group 2 (ESTRI) of ICH.
MAA	Marketing Authorization Application
MHLW	Ministry of Health, Labour and Welfare
Macro	Automation of several steps within a computer program (e.g. MSOffice)
NCA	National Competent Authority
NeeS	Non-eCTD electronic Submission. See "Guidance for Industry on Providing Regulatory Information in Electronic Format: NeeS" (This document is published under the auspices of the EU Telematic Implementation Group - electronic submissions (TIGes))
Network	A communication system that connects different computers and enables them to share peripherals such as printers, disk drives and databases. Users (clients) can access applications and databases connected by the network.

Term	Definition
Node	Represents a single node in an XML-tree: The unit of an eCTD tree where other nodes or leafs can be added.
Node Extension	The extension of the definition of an element beneath a defined table of contents tag.
OCR	Optical Character Recognition: electronic conversion of scanned images into machine-encoded text
Pdf	Portable Document Format, a proprietary (Adobe Systems) de facto standard for the electronic transfer of documents.
Publishing	Procedure to make dossiers available out of an SMS software
QA	Quality Assurance
QOS	Quality Overall Summary
Rft	Rich Text Format: a cross-plattform format for text documents
SaaS	Software as a Service
SAP	SAP software platform
Sequence number	Unique number of a submission within a dossier
SMS	Submission Management System
SOP	Standard operating Procedure
Submission	Compiled documentation sent out to authority
TIGes	EU Telematic Implementation Group - electronic submissions
URS	User Requirement Specification
VPN	Virtual private Network - secure internet connection
XML	Extensible Markup Language. An ISO standard for describing structured information in a platformindependent manner.
xml backbone	Table of Content for an eCTD-submission

ANNEX 2: REFERENCES AND LINKS TO WEBPAGES ABOUT e-CTD REQUIREMENTS

Reference 1 : EDQM – PA/PH/CEP (09) 108

Guidance for Submission of Electronic Documentation for Applications for Certificates of Suitability (CEPs): Revised Procedures (PA/PH/CEP (09) 108)

http://www.edqm.eu/en/certification-new-applications-29.html

Reference 2 : EDQM – PA/PH/CEP (09) 109, 1R

Updated EDQM procedures related to Paper and Electronic Submissions for CEP applications (PA/PH/CEP (09) 109, 1R)

http://www.edqm.eu/en/certification-new-applications-29.html

Reference 3 : EMA – EMA: eSubmissions (general)

http://esubmission.ema.europa.eu/doc/index.html

Reference 4 : **CMDh/085/2008/rev9 November 2012**

Requirements on submissions for new Applications within MRP, DCP or National procedures : CMDh-085-2008-Rev09-2012

Reference 5 : FDA: eSubmissions (general)

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

Reference 6 : eCTD sample submission

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Reference 7 : pre-assigned number

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

Reference 8: eCTd submission

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Reference 9 : **Guidance for Industry**

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126961.pdf

Reference 10: ICH Topic M 4

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002721.pdf

Reference 11 : ICH M2 EWG – eCTD specifications

ICH M2 EWG Electronic Common Technical Document Specification version 3.2.2.

http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf

Reference 12 : EMA/43526/2010 V.1.0

EMA/43526/2010 V.1.0 Practical Guidelines on the use of the eCTD format for ASMFs for Active Substance Master File Holders and Marketing Authorization Holders

http://esubmission.ema.europa.eu/doc/index.html

Reference 13: TIGes Harmonised Guidance for eCTD Submissions in the EU

TIGes Harmonised Guidance for eCTD Submissions in the EU Version 2.0, August 2011

http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20Document%202%200_2011_TIGes%20adoped%20for%20publication.pdf

Reference 14 : FDA : Comprehensive Table of Contents Headings and Hierarchy

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf

Reference 15 : FDA Guidance for Industry

Providing regulatory submissions in electronic format – human pharmaceutical product applications and related submissions using the eCTD specifications – October 2005

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126961.pdf

Reference 16 : FDA : portable document format specifications

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163179.pdf

Reference 17 : EMA: implementation of electronic submission – December 2008

EMEA/572459/2008: EMEA Implementation of Electronic-Only Submissions and Mandatory eCTD Submissions in the Centralised Procedure: Statement of Intent

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004098.pdf