Review Article

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH M2 EWG, Electronic Common Technical Document

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Accepted on: 28-06-2014; **Finalized on:** 31-08-2014.

ABSTRACT

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by regulatory authority in any country. Once preclinical and clinical trial data have been collected, a New Drug Application (NDA) must be submitted to the regulatory authority for approval. Although the requirements for this submission have similarities around the world, until now, the applications have been different. Till date, the applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses. Thus, a common format of submission will help in overcoming these hurdles. Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, Europe Union and United States. The ECTD is the electronic equivalent to the CTD. It has been developed by the ICH M2 Expert Working Group (EWG). ICH ECTD is an internationally driven standard designed to reduce cost in the administration, assessment and archiving of applications for marketing authorization of medicinal product for human use, to reduce the use of paper and streamline the assessment process making the system more efficient.

Keywords: CTD, ECTD, EWG, ICH, NDA.

INTRODUCTION

The ICH[1] M4 Expert Working Group (EWG) has defined the common technical document (CTD).The ICH M2 Expert Working Group (EWG) has defined, in the current document, the specification for the Electronic Common Technical Document (ECTD). The ECTD is defined as an interface for the industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission. The ECTD (Electronic Common Technical Document) specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority. Industry to industry and agency to agency transfer is not addressed.

The specification for the ECTD (Electronic Common Technical Document) is based upon content defined within the CTD (Common Technical Document) issued by the ICH (International Conference on Harmonization) M4 EWG (Expert Working Group).The CTD (Common Technical Document) describes the organization of modules, sections and documents. The structure and level of detailed specified in the CTD (Common Technical Document) have been used as the basis for defining the ECTD (Electronic Common Technical Document) structure and content but, where appropriate, additional details have been developed within the ECTD (Electronic Common Technical Document) specification.

The philosophy of the ECTD (Electronic Common Technical Document) is to use open standards. Open standards, including proprietary standards which through their widespread use can be considered de facto standards, are deemed to be appropriate in general.

The CTD (Common Technical Document)[2] as defined by the M4 EWG (Expert Working Group) does not cover the full submission that is to be made in a region. It describes only modules 2 to 5, which are common across all regions. The CTD (Common Technical Document) does not describe the content of module, the regional administrative information and prescribing information, nor does it describe documents that can be submitted as amendments or variations to the initial application. The value of producing a specification for the creation of an electronic submission based only upon the modules described in the CTD (Common Technical Document) would be limited. Therefore, the M2 EWG (Expert Working Group)[3] has produced a specification for the ECTD (Electronic Common Technical Document) that is applicable to all modules of initial registration applications and for other submissions of information throughout the life cycle of the product, such as variations and amendments.

This document describes the parts of the registration application that are common to all regions and some of the life cycle requirements for products. The parts of the registration application that are specific to a region will be covered by regional guidance. However, this backbone has been developed to handle both the regional and common parts of submission.

MATERIALS AND METHODS

Appendix I: Overall architecture

Guiding design principles

This appendix defines the basic principles that drove the design and architecture of the ECTD (Electronic Common Technical Document). Detailed specifications are defined in appendices 2.

Business model

The business process to be supported can be described as follows:

Industry <----> Message <----> Agency <----->

The business process defines specific requirements for the message. The ECTD (Electronic Common Technical Document) specification currently provides only a transport mechanism for one-way traffic from applicant to agency. The primary focus of the ECTD (Electronic Common Technical Document) is to provide a data interchange message between industry and agencies. Industry initiates the process by creating the initial submission in terms of an electronic CTD (Common Technical Document). Throughout the life cycle of this process, additional information will be submitted to update or modify the information contained in the initial submission (e.g. supplement, amendment, variation.) The agency can submit acknowledgements, queries and requests to industry. These are considered simple messages using electronic mail or other transport formats. The overall architecture of the ECTD (Electronic Common Technical Document) is designed to provide a commonly agreed upon submission and submission structure that imposes minimal restriction to the industry and agencies.

Modular structure of the ECTD

The structure of the electronic submission in terms of organization and navigations should be consistent with the modular structure of Common Technical Document. The goal of this design principle is to standardize the electronic format of the common parts of the ECTD (Electronic Common Technical Document).

XML based ECTD

The XML (Extensible Markup Language)[4] ECTD (Electronic Common Technical Document) DTD (Document type definition) defines the overall structure of the submission. The purpose of XML (Extensible Markup Language) backbone is two-fold: (1) to manage meta-data for the entire submission and each document within the submission and (2) to constitute a comprehensive table of contents and provide corresponding navigation aids. Meta-data on submission level include information about submitting and receiving organization, manufacturer, publisher, ID and kind of the submission, and related data items. Examples for meta-data on document level are versioning information, language, descriptive information such as document names and checksums.

The XML (Extensible Markup Language) instance of any submission should be created and validated according to the XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) DTD (Document Type Definition).

The XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) DTD (Document Type Definition) describes the hierarchical structure according to the CTD (Common Technical Document) as defined by the ICH (International Conference on Harmonization) M4 Expert Working Group. It includes multiple hierarchical levels depending on the specific modules as defined in the CTD (Common Technical Document). The actual submission can include more hierarchical levels below those defined in the CTD (Common Technical Document). The XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) instance covers the entire submission including all the hierarchical levels and includes references to each individual file.

The submission should include a style sheet that supports presentation of the XML instance, navigation according to the table of contents, and provide access to all documents within the submission. A standard style sheet for viewing the ECTD (Electronic Common Technical Document) submission is defined and provided by the ICH (International Conference on Harmonization) M2 EWG (Expert Working Group). Presentation and navigation via other style sheets on the receiving side should be possible. Consult regional authorities on the acceptability of submitting non-ICH (International Conference on Harmonization) style sheets.

Multiple region support

The scope of each submission is global according to the Common Technical Document, meaning that modules 2 through 5 of a submission are intended for all regions with the exception of selected documents (e.g., in the quality module), which have a regional scope. Module 1 of a submission is regional in nature.

Life cycle management

The applicant creates a submission that is stored in a local repository. The applicant submits the initial submission to the agency, which imports the submission into another local repository. The nature and kind of the local repositories is not within the scope of the ECTD (Electronic Common Technical Document). The initial submission should be self-contained, meaning that it includes all documents and no references to other submissions. Regional guidance should be consulted if references to other submissions are needed.

Following the initial submission, the applicant can submit incremental updates such as amendments and variations. Updates can refer to documents in the previous submissions. Updates should be designed in a way that

they can be loaded into the repository by fully preserving the initial or previous submission via version control. The XML (Extensible Markup Language) backbone should include meta-data identifying the update and providing navigation aids to filter for different submission types.

It is preferred that when a common technical document is submitted electronically, the entire submission be in electronic format with the exception of certain regional forms that currently require written signatures. See appendix 5 for regional requirements.

Appendix 2: The ECTD submission

Introduction

This appendix specifies the information technology aspect of the ECTD (Electronic Common Technical Document) submission. Informally, the ECTD (Electronic Common Technical Document) submission is a directory structure with files including the XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) instance, reports, data and other submission information. The ECTD (Electronic Common Technical Document) submission supports multilingual and multi-region aspects.

The ECTD submission

An ECTD submission[4] is a collection of data objects that follows the ECTD (Electronic Common Technical Document) specification. The main function of the ECTD (Electronic Common Technical Document) submission is data exchange. Information systems would need to be developed to process the ECTD (Electronic Common Technical Document) submission. The biggest benefits are expected when the ECTD (Electronic Common Technical Document) submission is loaded into an information system that supports the review process.

However, one can view an ECTD (Electronic Common Technical Document) submission with a web browser as it is web ready.

The ECTD submission is composed of the following:

1) Directory structure
2) XML ECTD instance
3) Content files

Directory structure

The directory structure is a structure of directories and files. There should be a reasonable maximum number of entries (directories and files) per directory. The directory structure should follow the rules below. The files could be in several formats as specified below.

The name of the files and directories are identifiers. They should be short. The file names are not intended to convey meta-data, though some meaning in the name helps (i.e. no random names)

Recommended, but optional, names for directories and files are provided in appendix 4. Any directory names and file names that are added to the ECTD (Electronic Common Technical Document) submission by the applicant should be descriptive, logical and brief.

XML ECTD instance

The instance is in the submission sequence number directory. The submission sequence number directory should contain at least two files and one or more directories. One of the files in the submission sequence directory should be the instance and the other should be the MD5 checksum of the instance. The instance is the starting file for the processing by an XML (Extensible Markup Language) processor.

The intention is to have links from the leaf elements of the instance to the files in the ECTD (Electronic Common Technical Document) submission as opposed to creating a single XML (Extensible Markup Language) document that contains the entire ECTD (Electronic Common Technical Document) submission. The instance also contains meta-data at the leaf level.

ECTD template

The ICH (International Conference on Harmonization) website (http://estri.ich.org/eCTD) includes an empty ECTD (Electronic common Technical Document) folder template as an example of an ECTD (Electronic Common Technical Document) submission folder structure. It shows all of the possible modules 2-5 folders as defined in appendix 4 and can be populated with the applicant data and edited as appropriate (i.e. adding additional folders or removing unnecessary folders). The applicant should still add the relevant regional module 1 folders and content, add the appropriate utility folders and content, and create the XML (Extensible Markup Language) index files to complete a valid ECTD (Electronic Common Technical Document) submission.

Formats

Formats should be readable at least for as long as it is needed for the regulatory process. This process could be very long (e.g., 50 years). These points to the advantage of neutral formats: formal standard, industrial page 2-2 standard, vendor independent, and text- like. The format should be adapted to the type of data.

The list of agreed to formats will be updated as technology evolves and new requirements arise. XML (Extensible Markup Language) will be preferred for all type of data.

Common formats

The common formats that can be included in an ECTD (Electronic Common Technical Document) submission are:

1) Narrative: Portable Document Format (PDF)
2) Structured: Extensible Markup Language (XML)

3) Graphic: whenever possible, use PDF. When appropriate or when PDF is not possible, use Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG) and Graphics Interchange format (GIF). Special formats for very high resolutions could be appropriate on a case by case basis.

Regional use of other formats

Regulatory authorities and applicants could agree to use other formats regionally (i.e., non common formats or uses of the common formats in a different way from above). The use of other formats is discouraged and the intention is to use as much as possible the common formats. The intention of the use of other formats is for transition.

There are two classes of transitions:

1) Legacy transition: from the past to the present (i.e. old formats to present)

2) Future transition: from the present to the future (i.e. from present formats to new formats). The new formats would normally be candidates for common formats.

Links

CTD (Common Technical Document) cross-references can be supported in the ECTD (Electronic Common Technical Document) through the use of hyperlinks. Links among the objects in the ECTD submission should be relative. The intention is to make the ECTD (Electronic Common Technical Document) submission self contained. All literature references introduced by the applicant should be included in the submission.

Presentations

Presentation is closely associated with formats. To associate a style sheet with a file usually one has to use a linking technology. The linking between style sheets (which could be in a separate file) and a data file should be relative. In addition, there is the dimension of media. One file could have several style sheets; the one used depends on the media. For example: there could be one presentation for the screen and another for paper.

Checksums

The ECTD (Electronic Common Technical Document) submission should contain checksums for each individual file including a checksum file for the ECTD (Electronic Common Technical Document) XML (Extensible Markup Language) instance. Initially, the MD_5 Message-Digest Algorithm (MD_5) should be used for this purpose. Including a checksum for each individual file provides a number of benefits including:

1) The integrity of each file can be verified by comparing the checksum submitted with the file and the computed checksum.

2) The checksum can be used to verify that the file has not been altered in the historical archive of the regulatory authority. This is especially useful as the files are migrated from one storage medium to another, as in the case of backup to magnetic tape storage.

Element to file directory mapping

The following rules are recommended:

1) The rules below for the file and directories take precedence

2) Add the corresponding extension to the file

3) If appropriate, use a reasonable abbreviation

Appendix 3: General considerations for the CTD modules

Introduction

Documents that are provided in the different modules should be formatted as defined by the ICH (International Conference on Harmonization) common technical document. There should also be consistency in the way navigational aids are provided. Within each document, bookmarks and hypertext links from the table of contents should be provided to all tables, figures, publications, and appendices.

Hypertext links should be provided throughout the body of these documents to aid efficient navigations to annotations, related sections, publications, appendices, tables, and figures that are not located on the same page. CTD (Common Technical Document) cross-references can be supported in the ECTD (Electronic Common Technical Document) through the use of hyperlinks. If a list of references is included at the end of a document, there should be hypertext links to the appropriate publication.

Documents should be generated from electronic source documents and not from scanned material, except where access to the source electronic file is unavailable or where a signature is called for.

Folder and naming conventions

Recommended, but optional, folder and file names are presented in this specification. These could be used in most cases; however applicants can modify this specification where appropriate. For example, it is generally acceptable to include an additional folder for information where an appropriate folder name is unavailable in the ECTD (Electronic Common Technical Document) specification or to provide for additional file organization where the recommended foldering is inadequate. It is recommended that applicants maintain folder names listed in this specification. Folder and file naming conventions are represented in the table 1.

This should not be interrupted to mean that the actual ECTD (Electronic Common Technical Document) XML (Extensible Markup Language) DTD (Document Type Definition) should be changed or altered in any way.

Table 1: Folder and file naming convention

Description	File name
Study report 1	Study report-1.pdf
Study report 2	Study report-2.pdf
….	….
Study report 3	Study report-3.pdf

The maximum length of the name of a single folder or file is 64 characters including the extension. Folders or file names should be written in lower case only. All files should have one and only one file extension. The file extension should be used to indicate the format of the file. More details on the naming conventions are given in Appendix 2, and examples in Appendix 4.

File names provided in the ECTD (Electronic Common Technical Document)[5] are optional. To assist the reviewer when several similar files are open at the same time, it can be considered alternative naming conventions that could provide unique, understandable file names. The general provisions for naming of files are in Appendix 2, of the specification.

Typically, the file name would be the applicants internal numbering or naming convention for the studies. The following table gives an example of how files could be named.

Screenshots and folder hierarchy

Screenshots are provided in the following chapters of all modules down to the level of hierarchy as described in this appendix. In a web browser the content will appear in the order of the CTD (Common Technical Document) table of contents.

Detailed options on the folders and files are provide in Appendix 4 in case the applicant chooses to submit more granular documents. It is not mandatory to use the full folder hierarchy. Empty directories can be omitted; however, when the content is expected, justification should be provided as to why it is missing in accordance with the regional guidance.

Module 1-Administrative information and prescribing information

The name of the folder for module 1 should be m1.This module contains administrative information that is unique for each region. Regional guidance will provide the specific instructions on how to provide the administrative formats and detailed prescribing information.

Module 2-Summaries

The files in this module should be provided as PDF (Portable Document Format) text with exception of a few embedded images, when needed. The name of the folder for module 2 should be m2.The folder in this module 2 should be named as follows but can be further reduced or omitted to minimize path length issues. Folder hierarchy for module 2 is represented in table 2.

Table 2: A representative folder hierarchy for module 2

Section in CTD	Description	Folder name
2.2	Introduction	22-intro
2.3	Quality overall summary	23-qos
2.4	Nonclinical overview	24-nonclin-over
2.5	Clinical overview	25-clin-over
2.6	Nonclinical written and tabulated summaries	26-nonclin-sum
2.7	Clinical summary	27-clin-sum

Module 3-Quality

The name of the folder for module 3 should be m3. The folders in the module 3 should be named as follows but can be further reduced or omitted to minimize path length issues. Folder hierarchy for module 3 is represented in module 3.

Table 3: A representative folder hierarchy for module 3

Section in CTD	Description	Folder name
3.2	Body of data	32-body-data
3.2.S	Drug substance	32s-drug-subs
3.2.S	Drug substance [drug substance name] [manufacturer]	Substance-1-manufacturer-1
3.2.S.1	General information (name, manufacturer)	32s1-gen-info
3.2.S.2	Manufacture (name, manufacturer)	32s2-manuf
3.2.S.3	Characterization (name, manufacturer)	32s3-charac
3.2.S.4	Control of drug substance (name, manufacturer)	32s4-contr-drug-sub
3.2.S.4.1	specification (name, manufacturer)	32s41-spec
3.2.S.4.2	Analytical procedures (name, manufacturer)	32s42-analyt-proc
3.2.S.4.3	Validation of analytical procedures (name, manufacture)	32s43-val-analyt-proc
3.2.S.4.4	Batch analysis (name, manufacture)	32s44-batch-analys
3.2.S.4.5	Justification of specifications (name, manufacturer)	32s45-justif-spec
3.2.S.5	Reference standards or materials (name, manufacturer)	32s5-ref-stand
3.2.S.6	Container closure systems (name, manufacturer)	32s6-cont-closure-sys

Table 3: A representative folder hierarchy for module 3 (Continued.....)

Section in CTD	Description	Folder name
3.2.S.7	stability (name, manufacturer)	327-stab
3.2.P	Drug product (name, dosage form)	32p-drug-prod
3.2.P.1	Description and composition of the drug product (name, dosage form)	32p1-desc-comp
3.2.P.2	Pharmaceutical development (name, dosage form)	32p2-pharm-dev
3.2.P.3	Manufacture (name, dosage form)	32p3-manuf
3.2.P.4	Control of excipients (name, dosage form)	32p4-contr-excip
3.2.P.4	Control of excipients (name, dosage form)-excipient 1	Excipient 1
3.2.P.5	Control of drug product (name, dosage form)	32p5-contr-drug-prod
3.2.P.5.1	Specification(s) (name, dosage form)	32p51-spec
3.2.P.5.2	Analytical procedures (name, dosage form)	32p52-analyt-proc
3.2.P.5.3	Validation of analytical procedures (name, dosage form)	32p53-val-analyt-proc
3.2.P.5.4	Batch analysis (name, dosage form)	32p54-batch-analys
3.2.P.5.5	Characterization of impurities (name, dosage form)	32p55-charac-imp
3.2.P.5.6	Justification of specifications(name, dosage form)	32p56-justif-spec
3.2.P.6	Reference standards or materials (name, dosage form)	32p6-ref-stand
3.2.P.7	Container closure systems (name, dosage form)	32p7-cont-closure-sys
3.2.P.8	Stability (name, dosage form)	32p8-stab
3.2.A	Appendices	32a-app
3.2.A.1	Facilities and equipments (name, dosage form)	32a1-fac-equip
3.2.A.2	Adventitious agents safety evaluation (name, dosage form, manufacturer)	32a2-advent-agent
3.2.R	Regional information	32-reg-info
3.3	Literature references	33-lit-ref

Module 4 - nonclinical study reports

The name of the folder for module 4 should be m4[5]. The folders in module 4 should be named as follows but can be further reduced or omitted to minimize path length issues. Folder hierarchy for module 4 is represented in table 4.

Table 4: A representative folder hierarchy for module 4

Section in CTD	Description	Folder name
4.2	Study reports	42-stud-reports
4.2.1	pharmacology	421-pharmacol
4.2.1.1	Primary pharmacodynamics	4211-prim-pd
4.2.1.2	Secondary pharmacodynamics	4212-sec-pd
4.2.1.3	Safety pharmacology	4213-safety-pharmacol
4.2.1.4	Pharmacodynamic drug interactions	4214-pd-drug-interact
4.2.2	Pharmacokinetics	422-pk
4.2.2.1	Analytical methods and validation reports (if separate reports are available)	4221-analyt-met-val
4.2.2.2	Absorption	4222-absorp
4.2.2.3	Distribution	4223-distrib
4.2.2.4	metabolism	4224-metab
4.2.2.5	Excretion	4225-excr
4.2.2.6	Pharmacokinetic drug interactions (nonclinical)	4226-pk-drug-interact
4.2.2.7	Other pharmacokinetics studies	4227-other-pk-stud
4.2.3	Toxicology	423-tox
4.2.3.1	Single dose toxicity (in order by species, by route)	4231-single-dose-tox
4.2.3.2	Repeat dose toxicity (in order by Species, by route, by duration including supportive toxicokinetics evaluations)	4232-repeat-dose-tox
4.2.3.3	Genotoxicity	4233-genotox
4.2.3.3.1	*In vitro*	42331-in vitro
4.2.3.3.2	In vivo (including supportive toxicokinetics evaluations)	42332-in vivo
4.2.3.4	Carcinogenicity (including supportive toxicokinetics evaluation)	4234-carcigen

Table 4: A representative folder hierarchy for module 4 (Continued.....)

Section in CTD	Description	Folder name
4.2.3.4.1	Long term studies (in order by species, including range-finding studies that cannot be appropriately included under repeat dose toxicity or pharmacokinetics)	42341-lt-stud
4.2.3.4.2	Short or medium term studies (including range-findings that cannot be appropriately included under repeat dose toxicity or pharmacokinetics)	42342-smt-stud
4.2.3.4.3	Other studies	42343-other-stud
4.2.3.5	Reproductive and developmental toxicity (including range-findings studies and supportive toxicokinetics evaluations)	4235-repro-dev-tox
4.2.3.5.1	Fertility and early embryonic development	42351-fert-embryo-dev
4.2.3.5.2	Embryo-fetal development	42352-embryo-fetal-dev
4.2.3.5.3	Prenatal and postnatal development, including maternal function	42353-pre-postnatal-dev
4.2.3.5.4	Studies in which offspring (juvenile animals) are dosed and/or further evaluated	42354-juv
4.2.3.6	Local tolerance	4236-loc-tol
4.2.3.7	Other toxicity studies (if available)	4237-other-tox-stud
4.2.3.7.1	Antigenicity	42371-antigen
4.2.3.7.2	Immunotoxicity	42372-immunotox
4.2.3.7.3	Mechanistic studies (if not included) (Elsewhere)	42373-mechan-stud
4.2.3.7.4	Dependence	42374-dep
4.2.3.7.5	Metabolites	42375-metab
4.2.3.7.6	Impurities	42376-imp
4.2.3.7.7	Other	42377-other
4.3	Literature references	43-lit-ref

Module 5-clinical study reports

The name of the folder for module 5 should be m5. The folders in the module 5 should be named as follows but can be further reduced or omitted to minimize path length issues. Folder hierarchy for module 5 is represented in table 5.

Table 5: A representative folder hierarchy for module 5

Section in CTD	Description	Folder name
5.2	Tabular listing of all clinical studies	*52-tab-list*
5.3	Clinical study reports	*53-clin-stud-reports*
5.3.1	Reports of Biopharmaceutics studies	531-rep-biopharm-stud
5.3.1.1	Bioavailability (BA) study reports	5311-ba-stud-reports
	“study report 1”	Study-report-1
	“study report 2”	Study-report-2
	“study report 3”	Study-report-3
5.3.1.2	Comparative BA and bioeqvivalence (BE) study reports	5312-compar-ba-be-stud-rep
	“study report 1”	Study-report-1
	“study report 2”	Study-report-2
	“study report 3”	Study-report-3
5.3.1.3	In vitro-in vivo correlation study reports	5313-in-vitro-in-vivo-corr-stud-rep
	“study report 2”	Study-report-2
	“Study report 1”	Study-report-2
5.3.1.4	“study report 3”	Study-report-3
5.3.1.4	Reports of bioanalytical and analytical methods for human use	5314-bioanalyt-analyt-met
	“study report 1”	Study-report-1
	“study report 2”	Study-report-2
	“study report 3”	Study-report-3
5.3.2	Reports of studies pertinent to pharmacokinetics using human biomaterials	532-rep-stud-pk-human-biomat
5.3.2.1	Plasma protein binding study reports	5321-plasma-prot-bind-stud-rep
	“study report 1”	Study-report-1
	“study report 2”	Study-report-2
	“study report 3”	Study-report-3
5.3.2.2	Reports of hepatic metabolism and	5322-rep-hep-met-drug-
	Drug interaction studies	Interact-stud
	“study report 1”	Study-report-1
	“study report 2”	Study-report-2

Section in CTD	Description	Folder name
	"study report 3"	Study-report-3
5.3.2.3	Reports of studies using other human biomaterials	5323-stud-other-human-biomat
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.3	Reports of human pharmacokinetics (PK) studies	533-rep-human-pk-stud
5.3.3.1	Healthy subject PK and initial	5331-healthy-subj-pk-init
	Tolerability study reports	Ol-stu-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.3.2	patient PK and initial tolerability study reports	5332-patient-pk-init-tol-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.3.3	Intrinisic factor PK study reports	5333-intrin-factor-pk-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.3.4	Extrinisic factor PK study reports	5334-extrin-factor-pk-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.3.5	Population PK study reports	5335-popul-pk-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.4	Reports of human pharmacodynamics (PD) studies	534-rep-human-pd-stud
5.3.4.1	Healthy subject PD and PD/PK study reports	Healthy-subj-pd-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.4.2	Patient PD and PK/PD study reports	5342-patient-pd-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3

Table 5: A representative folder hierarchy for module 5 (Continued.....)

Section in CTD	Description	Folder name
5.3.5	Reports of efficacy and safety studies	535-rep-effic-safety-stud
5.3.5.1	Study reports of controlled clinical studies pertinent to the claimed indication	5351-stud-rep-contr
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.5.2	Study reports of uncontrolled clinical studies	5352-stud-rep-uncontr
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.5.3	Reports of analyses of data from more than one study	5353-rep-analys-data-more-one-stud
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.3.5.4	Other study reports	5354-other-stud-rep
	"study report 1"	Study-report-1
	"study report 2"	study-report-2
	"study report 3"	Study-report-3
5.3.6	Reports of post marketing experience	536-postmark-exp
5.3.7	Case report forms and individual patient listings	537-crf-ipl
	"study report 1"	Study-report-1
	"study report 2"	Study-report-2
	"study report 3"	Study-report-3
5.4	Literature references	54-lit-ref

The CTD (Common Technical Language) organization provides locations for case report forms and individual patient data listings in module 5.3.7 and for literature references in module 5.4.

In the ECTD (Electronic Common Technical Document), files for publications and literature references should be located in the folder for module 5.4. however, in the index.xml file the leaf elements for these publications and literature references should be included under the same heading as the other study report files with additional information included through use of the study tagging file, if applicable in that region.

In addition, a repeat of the leaf element should be placed under the heading for 5.4 literature references.

Case report forms, data sets and individual patient data listing should be organized according to regional guidance.

Appendix 4: Region specific information including transmission and receipt

Introduction

This section describes region specific information for content that is not explicitly included in the common technical document and logistical details appropriate for the transmission and receipt of submissions using the electronic common technical document.

Region specific information: Module 1

This module contains administrative information that is unique for each region. There will be local requirements for both the content and electronic component of module 1[5]. The ECTD (Electronic Common Technical Document) backbone was developed to enable the transfer of the regional information included in a regulatory dossier.

Regional guidance will provide the specific instructions on how to provide the administrative forms and detailed prescribing information. Module 1 includes all administrative documents (e.g. forms and certifications) and labeling, including the documents described in regional guidance.

Not all regionally specific documents are included in module 1. Technical reports required for a specific region should be placed in modules 2 to 5. These reports should be included in the module most appropriate for the content of information provided.

Each region provides specific guidance on the format and content of the regional requirements of each module. Contact information for each region is represented in table 6.

Table 6: Contact information for each region

Region	Internet Address	Electronic mail contact
European Union	http://www.emea.europa.eu	esubmissions@emea.europa.eu
Food and drug administration, USA	www.fda.gov/cber www.fda.gov/cder	esubprep@fda.hhs.gov esub@fda.hhs.gov
Ministry of health, labour and welfare, Japan	http://www.mhlw.go.jp http://www.pmda.go.jp	ectd@pmda.go.jp
Health Canada	http://www.hc-sc.gc.ca	ereview@hc-sc.gc.ca

Submission Addresses

Submission should be sent directly to the appropriate regulatory authority. Information on how to send submissions to each regulatory authority can be found at the reference location. Regulatory authorities and reference locations are represented in table 7.

Media

Refer to regional guidance for appropriate media types.

Cover letters

Applicants should provide a cover letter as a PDF (Portable Document File) file (e.g. cover.pdf). A paper cover letter should also be included with non-electronic portions of the submission (such as forms with signatures or seals, and certifications). The cover letter should include:

1) A description of the submission including appropriate regulatory information.
2) A listing of the sections of the submission filed as paper, electronic, or both paper and electronic.
3) A description of the electronic submission including type and number of electronic media, appropriate size of the submission, and if appropriate, characteristics concerning the media (e.g. format used for DLT tapes) based on regional guidance.
4) A statement that the submission is virus free with a description of the software used to check the files for viruses.
5) The regulatory and information technology points of contact for the submission.

Table 7: Regulatory authorities and reference location

Regulatory Authority	Reference Location
EMEA, European Union and national agencies	http://www.emea.europa.eu http://www.hma.eu/
Ministry of Health, Labour and Welfare, Japan	http://www.mhlw.go.jp http://www.pmda.go.jp
Food and Drug Administration, United States of America	http://www.fda.gov/
Health Canada, Health Protection Branch, Canada	http://www.hc-sc.gc.ca

Transport

Secure data exchange over the internet is the recommended means for transporting submissions. However, until the regulatory authorities can develop secure electronic gateways, submissions should continue to be physically transported by courier or registered mail.

Security

An MD_5 checksum should be included for each physical file in the ECTD (Electronic Common Technical Document). The checksum enables the recipient to verify the integrity of each of the content files in the submission. Each leaf of the XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) instance contains the location and calculated checksum of each of the file.

A checksum of the XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) instance

should also be included. Applicants should name this checksum file index-md_5.txt and include it as a file in the same directory as the XML (Extensible Markup Language) ECTD (Electronic Common Technical Document) instance. Applicants should print the contents of the index-md_5.txt file and include the paper copy with the paper cover letter for the submission. A separate file containing the checksum of the regional index file is unnecessary as that file is referenced by a leaf element in the index.xm l file.

An applicant can provide the ECTD as an encrypted file in accordance with the ICH (International Conference on Harmonization) M2 recommendation 4.1, if he regulated body has implemented it. This solution enables the ECTD (Electronic Common Technical Document) to be encrypted and transferred over the internet (if internet receipt is implemented regionally) or to be encrypted on one of the approved physical media standards. The purpose of encryption is to protect the privacy of the confidential information and to ensure it is only available to the authorized receiver. Encryption is always appropriate when the ECTD (Electronic Common Technical Document) is sent via the internet.

Encryption is not considered necessary if the information is sent using a physical media, although encryption is an option. The applicant should assume all liability for the media until it is delivered to the regulatory authority.

Applicants should not include any file security settings or password protection for individual files in the ECTD (Electronic Common Technical Document). Applicants should allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. Internal security and access control processes in the regulatory authority should maintain the integrity of the submitted files.

Receipt

Upon arrival at the regulatory authority, the submission is archived according to local regulations. A read only copy of the submission is then made available to the review community in the regulatory authority. This is typically done by placing the copy on a network setter.

Acknowledgement: Each regulatory authority should acknowledge the receipt of the ECTD (Electronic Common Technical Document) submission according to the policy and procedure of the individual regulatory authority. Applicants should use the address in table 6 to find the guidance regarding acknowledgements.

CONCLUSION

The ECTD is defined as an interface for industry to agency transfer of regulatory information while at the same time the consideration of the creation, review, life cycle management and archiving of electronic submission. The ECTD (Electronic Common Technical Document) specification lists the criteria that will make an electronic submission technically valid. It provides immediate access to complete and up-to-date information. It facilitates evaluation and better visibility of the process. It reduces workload and better communication with industry.

Acknowledgment: I feel extremely great full to my esteemed guide *Dr.R.Suthakaran M.Pharm., PhD., DPMM., DPQCQAM., DCA., PGDIPR*. For his untiring help and constant appraisal of the present work he has been constant source of inspiration and has always encouraged scientific thinking and installed me a sense discipline in my work. I would like to express my heartfelt thanks to him for his valuable guidance.

I would like to convey my special thanks and express my deepest gratitude to my friends Ms.Swathi.P, Ms.Snigdha.B, Mr.Rashtrapal.D, Mr.Chaitanya Prasad.K.

REFERENCES

1. www.ich.org
2. www.ich.org/products/ctd.html
3. estri.ich.org/eCTD
4. ICH: M2: Electronic Common Technical Document (eCTD): step 5.
5. eCTD specification 3.2.2-estri.ICH (estri.ich.org/ectd/ectd-specification_v3_2_2.pdf)

Source of Support: Nil, **Conflict of Interest:** None.