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Review Article

ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD): A REVIEW OF HISTORY, BENEFITS OF IMPLEMENTING, CHALLENGES, MODULES, RISKS INVOLVED IN eCTD PUBLISHING AND QUALITY CONTROL

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ABSTRACT

Electronic Common Technical Document (eCTD) is a topic of increasing interest in the pharmaceutical environment. Electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information. Since June 2003, applicants have had the option of submitting an eCTD in parallel with the paper submission (Common Technical Document), following sign-off by the International Conference on Harmonisation Steering Committee of the eCTD Specification document at Step 4. It is designed to make regulatory submissions easier and more efficient for drug makers and for regulators. When it comes to eCTD submission, there continues to be differences among different countries and even ICH regions. The standardization that electronic submissions will bring will allow for much greater consistency not only for the regulators but also for organizations. 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. As the move from paper-based to eCTD submissions continues around the world, a multitude of challenges are to be faced regulatory departments. This paper describes eCTD History, Benefits of Implementing, Challenges, Modules, Risks involved in eCTD publishing and Quality Control.

Keywords: Electronic Common Technical Document, Benefits,Challenges, Modules.

1. INTRODUCTION

After decades of using paper, the goal is the electronic transfer of drug applications and their review across submission formats, procedures, and regions came in. Electronic Common Technical Document (eCTD) is a topic of increasing interest in the pharmaceutical environment. The eCTD is the electronic equivalent to the Common Technical Document (CTD) format. The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission. The eCTD 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. It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). In November 2003, the ICH M2 group revised the specification for the eCTD to version 3.2, which remains the current version. 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. It provides a common global standard for companies to electronically submit the quality, safety and efficacy information required for approval of a new drug to regulatory agencies in the United States(US),

European Union (EU), Canada and Japan etc. that imposes minimal restriction to the industry and agencies.[1,2]

The primary technical components are:

- A high level folder structure (required)
- An EXtensible Markup Language(XML) "backbone" file which provides metadata about content files and lifecycle instructions for the receiving system.
- An optional lower level folder structure (recommended folder names are provided in respective modules of the eCTD specification below)
- Associated document type definitions (DTDs) and style sheets that support the presentation and navigation

2. History

The steadiness of the submission format 'paper' in the past might not apply for the electronic submission formats in the future (six standards in the last 20 years - SEDAMM, MERS, MANSEV, CANDA, DAMOS, eCTD). Today submitting to ICH countries might be as eCTD, Non-eCTD electronic Submissions(NeeS), eSubmission or paper. Submissions to non-ICH countries offer even a greater variety of electronic or paper formats.

The concept of electronic regulatory submissions is not new, and has been evolving in America and Europe since the late 1980s. The Food and Drug Administration (FDA) and others has worked with electronic submissions for more than a decade

CANDA –(Computer Aided New Drug Application), Initiated in 1985 by FDA in US. It was seen as a way for FDA reviewers to have rapid access to report and data together, in a format that allowed efficient and high-quality analysis of data. Unfortunately, the CANDA era led to a proliferation of unique and proprietary formats for CANDAs, most of which required a stand-alone desktop computer on the desk of each regulatory reviewer. A whole variety of strategies for CANDAs emerged, from simple to complex. Each CANDA required a reviewer to learn a new system for accessing the data, a daunting task in many cases that few reviewers had time for. There were no standards for the structure of a CANDA and no common software platform or file format for the data. The results were mixed, many reviewers and sponsors were delighted with the efficient review that CANDAs provided, but others were unwilling to train on and use multiple different systems, sometimes simultaneously. The FDA soon called a halt to the unstructured CANDA era. But this was certainly not the end of the submission of electronic data.

- DAMOS-Drug Application Methodology with Optical Storage; Initiated by European regulatory Europe in 1989.
- SEDAMM - Soumission Electronique de Dossiers d'Autorisation de Mise sur le Marché; Initiated by France in 1993.
- MERS- Multiagency Electronic Regulatory Submission Project; Initiated by USA, Newzea land, and Australia in 1994.
- MANSEV - Market Authorisation by Network Submission and Evaluation; Initiated by UK, Denmark, France, Italy and EMEA in 1997.

In 1997, ICH M2 Expert Working Group (EWG) started working closely with M4 (CTD), the ICH guideline that presents the agreed upon common format for the preparation of a well structured Common Technical Document for applications that will be submitted to regulatory authorities. Simultaneously the FDA revealed the beginnings of a new method of electronic submission. The increasing volume of NDAs and the need for expedited review caused by the 1992 Prescription Drug User Fee Act (PDUFA) initiatives demanded that the FDA develop an approach for the efficient review of electronic data. The FDA was looking for a way to deal with the accumulating volumes of paper in its file rooms and the logistical problem of distributing sections of regulatory submissions to appropriate reviewers. By means of a series of guidance documents, the agency intended to carefully define the structure and technology that was acceptable for electronic submissions. In this way, the FDA could ensure a consistent set of electronic submission documents and reviewers could be comfortable that any electronically submitted data would be viewable in a familiar format. As a result, in 2002, eNDA and eANDA Guidance issued by FDA. Shortly after the first guidance documents were issued, electronic submission of New Drug Application(NDA) and Abbreviated New Drug Application(ANDA) documents became an emerging standard for many pharmaceutical sponsors, eliminating the need for manual printing, duplication, pagination, and other processes.

A significant milestone was the adoption in 2003 of the ICH eCTD Guideline v3.0 on the electronic Common Technical Document (eCTD), which is the electronic counterpart of the Common Technical Document (CTD; a harmonized structure and format for regulatory submissions). Following development

of eCTD by ICH which is a start of transition to standards based submission has provided support for all application types including IND, NDA, BLA, ANDA, and Master Files. After that in 2004, ICH eCTD Guideline v3.2 was implemented in all ICH regions, In 2006 Withdrawal of eNDA and eANDA guidances took place. [3]

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 active pharmaceutical ingredient (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.

Internationally, the eCTD has been required for Centralised Procedure applications to the European Medicines Agency (EMA) since 2010. Use of the format is also strongly encouraged in Canada, Japan and other developed markets around the globe. Therefore, anyone who works on drug regulatory submissions needs to understand the format well.

In the US, the 2012 reauthorization and update of the Prescription Drug User Fee Act (PDUFA), within the Food and Drug Administration Safety and Innovation Act (FDASIA), elevates the eCTD format to a requirement for all New Drug Applications (NDAs), Biologics License Application (BLAs) and Abbreviated New Drug Applications (ANDAs). It also will be required for most Investigational New Drug Applications (INDs) within the next few years, depending on when FDA finalizes the pending guidance document.

On May 5, 2015, the U.S. Food & Drug Administration published a final, binding guidance document requiring certain submissions in electronic (eCTD) format within 24 months. The projected date for mandatory electronic submissions is May 5, 2017 for New Drug Applications (NDAs), Biologic License Applications (BLAs), Abbreviated New Drug Applications (ANDAs) and Drug Master Files (DMFs).[4]

3. Benefits of Implementing eCTD and challenges

The standardization that electronic submissions will bring will allow for much greater consistency not only for the regulators but also for organizations. Both parties will benefit from reducing automation and storage costs by having all data in a common electronic environment that will also allow them to manage the documentation and oversee products more efficiently, eliminating difficulties with accessing, searching through and finding data in paper format. A common global standard for electronic submission of quality, safety and efficacy information provides such benefits as:

- Allows regulators to use computer-based tools such as searching, copying and pasting text, making the review process more efficient and can complete reviews online in less time than it would take offline, which also benefits sponsors.
- Streamlines review process allowing for multiple reviewers and therefore a more efficient review process
- Allows Reuse of documents and submission components with more ease for several different regions by sponsors,
- Enhance ability to efficiently organize, prepare and manage submission content
- Reduce storage costs associated with producing and storing paper dossiers
- Streamlines workflows in development, regulatory and marketing departments while increasing collaboration between teams.

Despite these benefits, the mandatory switch to eCTD presents companies with several challenges. The costs, both in initial capital and annual expense of building, validating and operating an electronic publishing system, together with the training and administration required to develop organizational competency, present a significant barrier to adoption. The effort required to establish and maintain an in-house system can be substantial, technical tools and a team of trained technical experts is typically required to document the requirements; research and evaluate options; procure, install, configure and test the system; and validate documentation and execute the full solution. While each organization's implementation project plan is different, a typical timeframe to complete the required steps is estimated to be between 9 – 18 months depending on the system size and configuration complexity. Another barrier to adoption is the risk of failed submissions. A deep knowledge of global regulatory requirements and the specifications of eCTD, as well as the ability to configure and operate a publishing platform to correctly assign every submission level and document-level attribute, is required to produce compliant submission documents. While large Pharma companies have the required capital and regulatory expertise for full

eCTD implementation, companies operating across their global business models in emerging markets may not, specifically when considering the dynamic nature of regulatory requirements across emerging and developed markets. The same can be said of small- to mid-sized Pharma companies operating in developed markets. For small - to mid-sized companies with modest annual submission requirements; it is clear that implementing an in-house system is difficult to justify.

Apart from the above, different implementation approaches, varied regional rules, changes in way of working, Granularity in eCTD, working with PDFs and hyperlinks, not ease to make Last minute changes are several other challenges.

Since the introduction of the eCTD, submissions to FDA using the format have continued to grow steadily. According to FDA, eCTD submissions to the agency have climbed each year since 2004. In fiscal 2007, they made up about 9% of NDAs. In fiscal 2014, eCTDs accounted for 85% of NDAs.

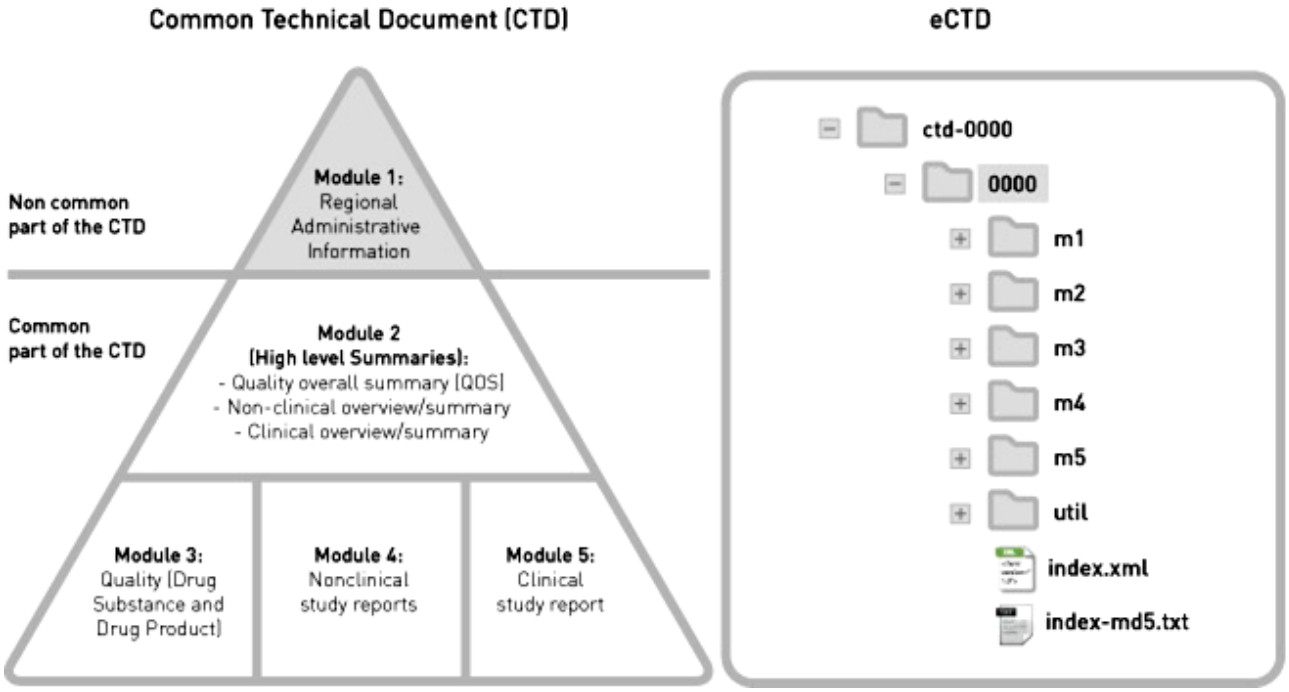
4. Modules of eCTD

The eCTD has five modules in two categories. There are

1. **Regional module which includes only Module 1** - Administrative information and prescribing information - not harmonized - different for each region; i.e., country, defined by each of the ICH regions(USA, Europe and Japan).
2. **Common modules: which includes module 2 – 5** (Harmonized - common to all the regions)
   - Module 2 - Common technical document summaries
   - Module 3 - Quality
   - Module 4 - Nonclinical study reports
   - Module 5 - Clinical study reports

The specification for the eCTD is based upon content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organization of modules, sections and documents. The structure and level of detail specified in the CTD have been used as the basis for defining the eCTD structure and content but, where appropriate, additional details have been developed within the eCTD specification.

The ICH website includes an empty eCTD folder template as an example of an eCTD submission folder structure. It shows all of the possible modules 2-5 folders 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.**Fig-1**



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. The eCTD backbone was developed to allow the transfer of the regional information included in a regulatory dossier. Regional guidance will provide the specific instructions on how to provide the administrative formats and detailed prescribing information.

Each region provides specific guidance on the format and content of the regional requirements of eachModule. Following Table (**Table 1**) provides contact information for each region.

Table 1:

Region	Internet address	Electronic mail contact
European Union	http://www.emea.eu.int	esubmission@emea.eu.int
FDA, USA	http://www.fda.gov/cber http://www.fda.gov/cder	Esubprep@cber.fda.gov esub@cder.fda.gov
Ministry of Health, Labour and Welfare, Japan	http://www.mhlw.go.jp http://www.nihs.go.jp	e-submission@nihs.go.jp
Health Canada	http://www.hc-sc.gc.ca/hpbdgps/therapeut	mike_ward@hc-sc.gc.ca

Module 2-Summaries

This module contains overall summaries of quality, non-clinical and clinical. 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:

Section inCTD	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

This module contains Quality aspects of the intended drug or medicinal product. 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 table3.

Table 3:

Section inCTD	Description	Folder Name
3.2	Body of Data	*32-body-data*
3.2.S	Drug Substance	*32s-drug-sub*
3.2.S	Drug Substance [Drug Substance Name] [Manufacturer][1]	*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	Characterisation (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, manufacturer)	*32s43-val-analyt-proc*
3.2.S.4.4	Batch Analyses (name, manufacturer)	*32s44-batch-analys*
3.2.S.4.5	Justification of Specification (name,manufacturer)	*32s45-justif-spec*

3.2.S.5	Reference Standards or Materials (name,manufacturer)	*32s5-ref-stand*
3.2.S.6	Container Closure System (name,manufacturer)	*32s6-cont-closure-sys*
3.2.S.7	Stability (name, manufacturer)	*32s7-stab*
3.2.P	Drug Product (name, dosage form) [2]	*32p-drug-prod*
3.2.P	Drug Product (name, dosage form) - *Name*	*product-1*
3.2.P.1	Description and Composition of the DrugProduct (name, dosage form)	*32p1-desc-comp*
3.2.P.2	Pharmaceutical Development (name, dosageform)	*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 Analyses (name, dosage form)	*32p54-batch-analys*
3.2.P.5.5	Characterisation of Impurities (name, dosageform)	*32p55-charac-imp*
3.2.P.5.6	Justification of Specifications (name, dosageform)	*32p56-justif-spec*
3.2.P.6	Reference Standards or Materials (name, dosageform)	*32p6-ref-stand*
3.2.P.7	Container Closure System (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 Equipment (name, manufacturer)	*32a1-fac-equip*
3.2.A.2	Adventitious Agents Safety Evaluation (name,dosage form, manufacturer)	*32a2-advent-agent*
3.2.A.3	Excipients- *Name* [3]	*32a3-excip-name-1*
3.2.R	Regional Information [4]	*32r-reg-info*
3.3	Literature References	*33-lit-ref*

[1] Each drug substance-manufacturer should be placed in a separate subordinate folder. Folders and files should be created for each drug substance-manufacturer section included in the submission in accordance with the hierarchy identified in the following chapters.

[2] Each drug product should be placed in a separate subordinate folder. Folders and files should be created for each drug product section included in the submission in accordance with the hierarchy identified in the following chapters. Reference should be made to regional guidance to determine whether the inclusion of multiple products within a single application is considered appropriate.

[3] The folder name should include the name of the Excipient, abbreviated as necessary to remain within the 64 character limit.

[4] This folder should be included where regional information is appropriate. Reference should be made to regional guidance for the types of information to be included in this section.

Module 4 - nonclinical study reports

This module contains details of nonclinical studies. The name of the folder for module 4 should be m45. 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:

Section	Description	Folder Name
4.2	Study Reports	*42-stud-rep*
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	*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 (Non-clinical)	*4226-pk-drug-interact*
4.2.2.7	Other Pharmacokinetic Studies	*4227-other-pk-stud*
4.2.3	Toxicology	*423-tox*
4.2.3.1	Single-Dose Toxicity (in order by species, byroute)	*4231-single-dose-tox*
4.2.3.2	Repeat-Dose Toxicity (in order by species, byroute, by duration, including supportivetoxicokinetics 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	*42332-in-vivo*
4.2.3.4	Carcinogenicity (including supportivetoxicokinetics evaluations)	*4234-carcigen*
4.2.3.4.1	Long-term studies (in order by species,including range-finding studies that cannot beappropriately included under repeat-dose toxicity or pharmacokinetics)	*42341-lt-stud*
4.2.3.4.2	Short-or medium-term studies (including range findingstudies that cannot be appropriatelyincluded under repeat-dose toxicity orpharmacokinetics)	*42342-smt-stud*
4.2.3.4.3	Other studies	*42343-other-stud*
4.2.3.5	Reproductive and Developmental Toxicity(including range-finding studies and supportivetoxicokinetics evaluations).(If modified studydesigns are used, the following subheadingsshould be modified accordingly)	*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,	*42353-pre-postnatal-dev*
4.2.3.5.4	Studies in which the offspring (juvenileanimals) are	*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

This module contains details of clinical studies. 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**.

Section inCTD	Description	Folder Name
5.2	Tabular Listing of all Clinical Studies	*52-tab-list*
5.3	Clinical Study Reports	*53-clin-stud-rep*
5.3.1	Reports of Biopharmaceutic Studies	*531-rep-biopharm-stud*
5.3.1.1	Bioavailability (BA) Study Reports	*5311-ba-stud-rep*
	"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 Bioequivalence (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 1"	*study-report-1*
	"Study Report 2"	*study-report-2*
	"Study Report 3"	*study-report-3*
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies	*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 toPharmacokinetics 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 DrugInteraction Studies	*5322-rep-hep-metab-interact-stud*
	"Study Report 1"	*study-report-1*
	"Study Report 2"	*study-report-2*
	"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 Pharmacokinetic (PK)Studies	*533-rep-human-pk-stud*
5.3.3.1	Healthy Subject PK and Initial TolerabilityStudy Reports	*5331-healthy-subj-pk-init-tol-stud-rep*
	"Study Report 1"	*study-report-1*
	"Study Report 2"	*study-report-2*
	"Study Report 3"	*study-report-3*
5.3.3.2	Patient PK and Initial Tolerability StudyReports	*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	Intrinsic 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	Extrinsic 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 Pharmacodynamic (PD) Studies	*534-rep-human-pd-stud*
5.3.4.1	Healthy Subject PD and PK/PD Study Reports	*5341-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*
5.3.5	Reports of Efficacy and Safety Studies	*535-rep-effic-safety-stud*
5.3.5	Reports of Efficacy and Safety Studies –*Indication Name*	*indication-1*
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 Postmarketing Experience	*536-postmark-exp*
5.3.7	Case Report Forms and Individual Patient Listings[1]	*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*

[1]The content of this folder should follow regional guidance.

5. e-CTD ready document

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.

a) File Organisation for the eCTD (Granularity)

Refer ICH Topic M 4 Common Technical Document for the Registration of Pharmaceuticals for Human Use. 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.

b) 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.

An ECTD submission is a collection of data objects that follows the eCTD (Electronic Common Technical Document) specification.

The ECTD submission is composed of the following:

- Directory structure
- XML ECTD instance
- 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.
The file formats included in this section are those formats that are commonly used in electronic submissions.

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

PDF
PDF is accepted as a standard for documents defined in this specification. Adobe Portable Document Format (PDF) is a published format created by Adobe. It is not necessary to use a product from Adobe or from any specific company to produce PDF documents. PDF is accepted as a standard for documents defined in this specification.
To ensure that PDF files can be accessed efficiently, PDF files should be no larger than 50 Megabytes. The files should be saved “optimized”.

Version
Agencies should be able to read all PDF files with version 4.0 or higher of the Acrobat Reader. Agencies should not need any additional software to read and navigate the PDF files.

Fonts
Agencies cannot guarantee the availability of any fonts except Times New Roman, Arial and Courier and fonts supported in the Acrobat product set itself. Therefore, all additional fonts used in the PDF files should be embedded to ensure that those fonts would always be available to the reviewer. When embedding fonts, all characters for the font should be embedded, not just a subset of the fonts being used

in the document. For narrating text: Times New Roman 12 and for Table Times New Roman 9-10 preferable.

Use of Colour fonts
The use of a black font colour is recommended. Blue font can be used for hypertext links.

Page Orientation
Pages should be properly oriented so that all portrait pages are presented in portrait and all landscape pages are presented in landscape.

Page Size and Margins
The print area for pages should fit on a sheet of A4 or Letter paper. A sufficient margin (at least 2.5cm) on the left side of each page should be provided in order to avoid obscuring information if the reviewer subsequently prints and binds the pages for temporary use. For pages in landscape orientation (typically tables and publications) smaller margins are allowable (at least 2.0cm at the top and 0.8cm left and right) so as to allow more information, displayed legibly. It is acceptable that header and footer information appears within these margins but not so close to the page edge that it may risk being lost upon printing.

Source of Electronic Document
PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents are more difficult to read and do not allow reviewers to search or copy and paste text for editing. They should be avoided where possible.

Methods for Creating PDF Documents and Images
The method used for creating PDF documents should produce the best replication of a paper document. To ensure that the paper and PDF version of the document are the same, the document should be printed from the PDF version. It is recommended that scanning be undertaken at a resolution of 300 dots per inch (dpi) to balance legibility and file size. Paper documents containing hand-written notes should be scanned at 300 dpi. Handwritten notes should be done in black ink for clarity.
For photographs, the image should be obtained with a resolution of 600 dpi. Gels and karyotypes should be scanned directly, rather than from photographs. Scanning should be at 600 dpi and 8-bit greyscale depth. Plotter output graphics should be scanned or captured digitally at 300 dpi. High-pressure liquid chromatography or similar images should be scanned at 300 dpi.

Hypertext Linking and Bookmarks
Hypertext links and bookmarks are techniques used to improve navigation through PDF documents. Hypertext links can be designated by rectangles using thin lines or by blue text. The bookmark hierarchy should be made identical to the table of contents with no additional bookmark levels beyond those present in the table of contents. The use of no more than 4 levels in the hierarchy is recommended.
When creating bookmarks and hyperlinks, the magnification setting *Inherit Zoom* should be used so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document.

Page Numbering
If a submission includes more than one document, no additional volume or page numbering is necessary. Only page numbers for individual documents are needed. Two exceptions to this rule can occur, details of which can be found in the guidance for the modules of the CTD.

- Firstly, where a document is split because of its size (e.g. >50MB), under which circumstances the second or subsequent file should be numbered consecutively to that of the first or preceding file.
- Secondly, where several small documents with their own internal page numbering have been brought together into a single file, under which circumstances it is not considered necessary to provide additional page numbering, but the start of each sub-document should be book marked.

Document Information Fields
Document information fields should not be used for the common portions of the eCTD, but they may be appropriate for some of the regional documents.

Open Dialog Box
The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page Layout* should be set as default.

Security
No security settings or password protection for PDF files should be included.

Indexing PDF Documents
Full text indices can be used to help find specific documents and/or search for text within documents. When a document or group of documents is indexed, all words and numbers in the file and all information stored in the Document Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat.

Use of Acrobat Plug-Ins
It is considered acceptable to use plug-ins to assist in the creation of a submission. However, the review of the submission should not require the use of any plug ins, in addition to those provided with Adobe Acrobat because Agencies should not be required to archive additional plug-in functionality.

XML Files
Information in an XML file is divided into specific pieces. These pieces are called objects or element types. The element type identifies the piece of information. For example, the name of the company submitting a registration application in eCTD format for review is identified with the element type <applicant>. All element type names are bracketed using the special characters <>. Inside the XML document, the element type name is placed just prior to the piece of information and after the information. This is called tagging.
By using a hierarchical structure, XML allows you to relate two or more elements. This is accomplished by nesting one element within another. Additional information about the element type is provided by attributes. Attributes are placed within the element types and are surrounded by " ". XML files are read by a parser found in internet browsers. Style sheets provide the browser with the information to create tables, fonts, and colours for display.

SVG Files
SVG is a language for describing two-dimensional graphics in XML. SVG allows for three types of graphic objects: vector graphic shapes (e.g., paths consisting of straight lines and curves), images and text. Graphical objects can be grouped, styled, transformed and composited into previously rendered objects. Text can be in any XML namespace suitable to the application, which enhances searchability and accessibility of the SVG graphics. The feature set includes nested transformations, clipping paths, alpha masks, filter effects, template objects and extensibility.[5-7]

6. Risks involved in eCTD publishing

As the move from paper-based to eCTD submissions continues around the world, a multitude of challenges faces regulatory departments. But there are simple steps you can take to avoid common problems, which at best can increase the cost of or cause delays to your submission's approval, and at worst result in receipt of a Refusal To File.
Your submission publishing might be conducted by a dedicated, in-house department located in the same office or on the other side of the globe, or you might utilize third-party service providers. Your publishers might be highly experienced regulatory consultants with chemistry degrees, or specialized staff with administrative, IT or creative backgrounds. Whatever the case, busy publishing teams typically encounter the following 10 problems. Find out what you can do to avoid these problems and prevent or at least mitigate the risks of your eCTD publishing project.

a) Source document incompatibility

Today's electronic publishing software greatly speeds up the publishing process by scanning source documents to automatically extract information to use as navigational aids in the published output. In this process, which differs among file types (Word, PDF, etc.) and tools from different vendors, source files are scanned and elements such as internal document links, existing bookmarks and heading/outline styles are processed and collected into the software's database to create bookmarks and hyperlinks in the published output.
If source files are not set up as the publishing software expects them to be, this process can be impaired and extra time may be required post publishing to manually add navigational elements. In companies

where the whole submission preparation process (stats, medical writing, regulatory affairs, publishing, quality control, etc.) is conducted in house, setting up strict procedures and templates ensures the success of this process. However, if any of these functions is conducted externally, challenges increase and it is worth considering the following tips:

- Set up and use standard procedures, templates and forms, and distribute these to any external service providers.
- Publishing departments/providers should document and distribute the specifications and expectations for source files to the concerned parties.
- Always ensure your source files are tested in the publishing software well before final publishing is scheduled.

b) Insufficient or conflicting information for publishers

Depending upon the experience of your regulatory affairs and publishing staff and the lines of responsibility between them, critical information required in the publishing process might be unclear or ambiguous to publishers even though it is included in the content of your submission. It is prudent to provide all expected information to the publisher, however obvious this information may seem.

By way of example, eCTD submissions rely heavily on the use of metadata, which provide additional information about elements. In some cases, these metadata are included in critical capacities such as folder paths in the final eCTD. Providing this information to publishers at the same time as the source files using well-designed procedures and forms is an easy way to prevent potential rework.

It is fairly safe to say that ambiguity is the publisher's biggest enemy. If information is missing, progress is usually halted while the information is sought. However, if information is provided, but is ambiguous or conflicting, there is a real risk of the publisher's interpreting the information incorrectly and the error may not be discovered until too late, requiring major rework.

c) Incorrect document versions

From a publisher's perspective, there is nothing more soul-destroying than working for days (or weeks) to complete publishing of a submission only to be informed that a wrong document or document version has been used. Unfortunately, all too often this means not only a large amount of rework but also the loss of full confidence in the integrity of the published submission, requiring more-intensive QC reviews.

Publishing groups that utilize closed document management systems (DMS) in their publishing workflows generally avoid this problem because only those documents and/or versions marked as approved are available for publishing. Groups that use file shares for publishing repositories are more susceptible to this type of problem and therefore require far more stringent procedures.

d) Short publishing timelines

Submission publishing usually occurs at the end of a very long process. Time lost in previous stages of the process often is expected to be recovered during publishing. This poses little problem to those with access to large publishing departments or providers that can simply add more resources to reduce the time required on critical path.

In smaller publishing operations where add- ing extra resources is not possible, aggressive timelines usually result in stressed publishers who are far more likely to produce error-laden submissions. It is sensible to allow extra time not only for the possibility of delay but also for other contingencies such as illness and problems with legacy files.

However, one of the most effective ways of mitigating risks to publishing timelines is to operate an incremental build policy, where modules or sections of your submission are published independently. Some parts of a submission normally are available for publishing weeks or even months before final publishing is scheduled to begin, and any possibility of publishing these sections outside the critical path will help adhere to the target time line.

e) Nonlinear delays

Not only are delays sometimes inevitable, (although they can be planned for, and in some cases mitigated), but they also can result in non- linear effects on the submission timeline.

For example, a delay of one or two days can be carried though the project and, if extra resources cannot be utilized, will result in a sub- mission that is one or two days late. But in other cases, especially where third-party providers are involved, delays of just a day or two may result in far more serious consequences. If the slot for publishing the project cannot be moved back by even a day or two due to conflicts with other scheduled projects, the one- or two-day delay may end up becoming a one- or two-week (or worse) delay.

f) Inappropriate granularity

It has often been said that that eCTD publish- ing begins with the author because a document produced using a quality template with the appropriate level of granularity has such a huge effect on publishing. If you plan to submit a section as multiple leaves, these leaves should be supplied as the corresponding number of source documents rather than being rolled up into a single file for splitting during publishing. Every source document that must be sent back for reformatting is another small opportunity for the project to be delayed.

g) Technical problems with legacy files

Because some information may be produced many years prior to inclusion in a submission using outdated software and equipment, many opportunities exist for errors to surface during publishing. Although legacy files may have been printed without issue in the past, electronic publishing is extremely efficient in highlighting technical issues, often at the most critical time.

These issues are generally not difficult to resolve, although they can be very time-consuming. Here, the most important tool in the publisher's toolbox is time, and by publishing submissions using incremental builds, these problems can be addressed well before they have opportunity to cause a delay.

h) Quality Controlreviewing at the right point

By the time publishing begins, source file con- tent should be final and approved, as changing a document during the publishing process can have a devastating effect on the project timeline. Set clear QC points throughout the project but ensure those points are appropriate to the task:

- All source documents should be quality checked before entering the publishing workflow.
- The submission structure (the assembly/outline) within the publishing software should be independently reviewed prior to publishing.
- All published PDF files should be reviewed on screen.
- Check bookmarks and links in published PDF files.
- Always validate and conformity-check eCTD submissions prior to submission.
- Independently check all submission media and packaging prior to sealing and dispatch.

i) Inappropriate validation process

One of the real advantages of the eCTD is the ability to check its technical conformity upon submission. This means that both the applicant and the agency can be sure - from a technical perspective that the eCTD conforms to the specifications of the guide- lines under which it is being submitted. Conformity can be determined within days, or even hours, of being submitted, rather than the weeks or sometimes months required with paper submissions.

But this process has another advantage. Although the eCTD is considered an open standard and can, in theory, be produced and viewed using software from any vendor, in most cases the actual software used by the agency is also available to the applicant. This means that prior to submitting your eCTD to, say, the European Medicines Agency, you can validate it using the same software the agency uses (EursValidator) and view the same conformity reports on which it bases acceptance of the submission. As long as the electronic transfer of the files to the agency does not introduce any corruptions, you can be 100% confident that your submission will be acceptable (from a technical perspective) to the agency.

j) Ineffective project management

There is no substitute for high-quality project management. This is no different in submission publishing than in any other area. A project cannot be expected to run smoothly and stay within budgetary and time constraints without careful management and clear communication.[5]

7. Quality eCTD Submissions

For an eCTD submission, it is imperative that the company works as a team to develop and submit quality documents refer **Table-6**, that are consistent with the guidances and internally consistent in terms. The scientists and the information systems professionals need to increase their understanding about each other's needs in order to successfully complete an e-submission. If necessary, essential training should be obtained so that your organization can remain competitive. Quality eCTD Submissions can save organization money, increase the accuracy of the submission and decrease review times, giving your company a competitive advantage. The basic principles for a successful and Quality eCTD Submissions are:

- **Early planning and preparation**
  with proper planning and preparation, companies can have a clear vision of a quality eCTD submission long before they put pen to paper or fingers to keyboard.

- **Knowing the regulatory science**
  knowledge of your molecule, the formulation, manufacturing process, analytical methods and specifications, as well as a thousand other details. In essence, key information needs to be consistent and repeated to assure continuity in the review process without making the reviewer backtrack and waste valuable time. As we put together a quality eCTD submission, we start with good science and knowledge of the reviewer's needs.

- **Understanding the guidance documents**
  FDA, International Conference on Harmonization (ICH) regulatory scientists and other regulators provide us with valuable insights into their needs. Key points from the guidances related to the submission must be communicated to all individuals contributing to the submission. It may appear that there are a hundred guidances with a thousand details, but in reality we digest this elephant one bite at a time.

- **Understanding the ICH CTD format and content specifications**
  ICH has recommended several file formats for the exchange of information. The associated specifications will be updated periodically. The guidance makes recommendations on general organizational issues related to the electronic submission of applications for human pharmaceutical products using the eCTD specifications. The eCTD specifications provide details on how to refer to an electronic file. One should understand and submit the electronic information for all files in the eCTD backbone files following the specifications associated with this guidance.

- **Watching consistencies successfully**
  Through practical workshop exercises, interactive discussions and real-life case studies, building eCTDs from the ground up will besuccessful. Taking Advice on industry's best practice, as well as submission pitfalls from the reviewer's perspective will be help the people in formulating the best strategies and employing the most practical tools to enhance the success of their electronic submissions.

- **Understanding XML (eXtensible Markup Language)**
  XML is a specification or standard that is used in eCTD submissions. XML enables an information provider (a regulatory submission from industry) and an information user (the regulatory authority) to create and exchange information. The content of information expressed in a markup language is often referred to as "meta data." Meta data provides fundamental information about the information being exchanged. Mark up languages or Meta data are typically used for three purposes: formatting, structuring data and data transport.

- **Knowing the e-submission process and the electronic backbone**
  The e-submission process starts long before you request your submission number from FDA. As stated previously, your e-submission process starts with knowing and using the guidances, knowing the CTD outline, following the content for each section/document, and watching for inconsistencies. With your first e-submission, FDA will probably suggest a sample number for your submission. If FDA does not make this suggestion, make the suggestion; request a sample submission number for your first couple of submissions. This is an excellent opportunity to work out the kinks in your process/system and open the communication channels with FDA. The sample submission does not take that much extra effort, is an excellent opportunity and is worth the investment e-submission process is outlined as followed:
    - ✓ Assemble the backbone.
    - ✓ Scan the non-electronic material.
    - ✓ Convert and parse the submission into PDF documents and place them into the backbone.
    - ✓ After parsing and PDFing, build the XML document using XMLSPY.
    - ✓ Ship the package—burn the CD and place the CD in a prepared folder with the hard copy cover letters.

- **Paying attention to lessons learned**
  Failure to pass the validation process will result in FDA refusing to receive the submission.People should focus on the practical experience gained, lessons learned, and the resulting best practices as the industry moves to a fully electronic submission paradigm.

- **Purchasing the right tools**
  Tools are available to automate the e-submission process and decrease the submission time through automation. When purchasing an electronic tool, include the requirements of three participants in the process: scientist, information systems professional regulators.Depending on the company size, potential hidden costs could include increased disk space, a database, a hash calculator, Adobe Acrobat, an XML authoring tool and a word processor. Remember, walk before you run. It is not advised to jump straight into a high-dollar, fully automated e-submission tool. There are plenty of smaller, completely capable tools that will enable you to walk before sprinting into a fully automated and more expensive tool.[8]

Table 6: Submission ready QC Checklist

Checklist for eCTD documents - Word Files			
#	**Criteria**	**Status**	**Comments**
1	Header and footer are not present or have been reduced to allow for Insight Overlay. (1" top, 0.75" bottom)	☐	
2	Font size 12 point for body text	☐	
3	Font size 9.5 – 10 point for tables	☐	
4	Page orientation follows legibility of body of document (i.e., landscape pages)	☐	
5	Page size is 8.5 x 11.0 or 11.0 x 8.5 (Letter size - portrait or landscape)	☐	
6	Hypertext links (for anything not located on same page)	☐	
7	Hypertext links for Tables of Contents in blue text with invisible rectangles	☐	
8	Hypertext links for scanned documents represented as blue text with invisible rectangles	☐	
9	Headings and subheading start with H1 and progress in order: H1, H2, H3, etc.	☐	
10	Document contains content, no blank or placeholder documents.	☐	
11	Absolutely NO Security on files	☐	
12	No files over 50 MB (best practice)	☐	
13	All headings, sub-headings, tables, and figures have the correct heading style applied.	☐	
14	Fonts used adhere to ICH recommended types	☐	
Checklist for eCTD documents - PDF Files			
#	**Criteria**	**Status**	**Comments**
1	No PDF Versions Over 7.0 or Under 4.0	☐	
2	Absolutely NO Security on files	☐	
3	No files over 50 MB (best practice)	☐	
4	Fonts used adhere to ICH recommended types	☐	
5	Font size 12 point for body text	☐	
6	Font size 9.5 – 10 point for tables	☐	
7	Formatting issues		
8	Pages mislocated		
9	Page orientation follows legibility of document. All pages have set to the page orientation for proper viewing of the document. Landscape pages must be rotated to make the text easily readable	☐	
10	Page size 8.5 x 11.0 or 11.0 x 8.5, No cropped PDF	☐	
11	If page size not exactly 8.5 x 11.0, printed text is still legible	☐	
12	Ample margins for pagination stamp(s) (1" top, .75" bottom)	☐	
13	All documents are clearly legible, that means there are no blurred pages, small font size, and smudged text when taken print out including especially Scanned documents.	☐	
14	All files are text searchable. This means document is rendered complete Optical Character Recognition for any scanned content.	☐	
15	All figures/graphs/tables/images which cannot be OCR is having title /alternative text which is text searchable.		
16	Scanned black & white are at 300 dpi	☐	
17	Hypertext links (for anything not located on same page) (i.e. for table, figure, document, section, etc)	☐	
18	Hypertext links for Tables of Contents in blue text with invisible rectangles	☐	
19	Hypertext links for documents represented as blue text with invisible rectangles. For inter-document links, it's preferred that the link opens the other document in a new window	☐	
20	Hypertext links for scanned document represented as rectangles with thin blue lines	☐	
21	Bookmarks and Hypertext links use relative path	☐	
22	Invalid Hypertext links	☐	
23	Insufficient hyperlinks (none or not enough)	☐	
24	Bookmarks reflect Table of Contents hierarchy	☐	
25	Bookmark matches the description/title showing on the TOC?		

26	Bookmark name indicate the bookmark's destination/content?		
27	Bookmark text, including capitalization, reflects text in document	☐	
28	Bookmarks text is spelled correctly without Spaces in the words	☐	
29	Is the bookmark way too long?		
30	Table of Contents* and Bookmarks for each and every document that is five (5) pages or longer.	☐	
31	Navigation tab is set to open to Bookmarks Panel and Page. If there are no bookmarks, navigation tab is set to Page Only. Page Layout and Magnification are being set to Default.	☐	
32	Truncated bookmarks contain ellipsis at end to indicate truncation	☐	
33	Truncation of bookmarks does not delete critical text of heading or caption	☐	
34	Bookmark text is black font	☐	
35	Bookmarks and Hypertext links magnification is set to Inherit Zoom	☐	
36	Page Numbering of document page = PDF page	☐	
37	Page stamp does not collide with text of document	☐	
38	Initial View when opening documents = Bookmarks & Page	☐	
39	Initial View opens to Table of Contents, even if not first page of document	☐	
	Document is set to Optimize for Fast Web View	☐	
checklist for eCTD submission			
#	**Criteria**	**Status**	**Comments**
1	Files Referenced in the XML Backbone(s)	☐	
2	eCTD Submissions Include Module 1	☐	
3	Application Numbers are 6 Digits	☐	
4	Sequence Numbers are 4 Digits	☐	
5	Ensure we receive what you intended	☐	
6	Do not send in one submission to be applied to multiple applications	☐	
7	XML must be Standard Components	☐	
8	PDF contains Recognizable Text	☐	
9	PDF Hyperlinks/Bookmarks are Correct	☐	
10	PDF Documents include TOCs	☐	

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