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ELECTRONIC DOSSIER REQUIREMENTS FOR USFDA

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ABSTRACT

The electronic common technical document (eCTD) is an interface and international specification for the pharmaceutical industry to agency transfer of regulatory information. The specification is based on the CTD format and was developed by the ICH Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). The Common Technical Document (CTD) describes the organisation of modules, sections and documents to be used by an Applicant for a Marketing Authorisation for a medicinal product for human use agreed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator. While the table of content is consistent with the harmonised CTD, the eCTD also provides a harmonised technical solution to implementing the CTD electronically. In other words, an eCTD is the submission of PDF documents, stored in the eCTD directory structure, accessed through the XML backbone and with the file's integrity guaranteed by the MD5 Checksum. The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). This Thesis describes the various types of submission types, Validation Criteria rules and documents required to submit a successful submission to USFDA through ESG WebTrader. The significance of electronic submissions to health authority is less manual work, accurate results and fast reviewing.

KEY WORDS: eCTD, ESG, FDA Meeting Requests, Orphan Drug Applications, INDs, NDAs, ANDAs, Annual Reports, amendments and supplements.

INTRODUCTION

The Electronic Common Technical Document (eCTD) is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) [1]. An eCTD submission has five modules: region-specific information, summary documents, quality-related information, nonclinical study reports, and clinical study reports.

When materials are submitted electronically, it is easier for FDA to review data, approve new drugs, and monitor drugs after they go on the market. Using eCTD also simplifies the process for submitters, because it is the same format used by drug regulatory agencies in other countries.

Starting in 2017, eCTD will be required for submissions to CBER and CDER. After the dates listed below, submissions that are not in eCTD format will not be filed or received unless exempted from the requirement.

Electronic submission requirements will apply to the following submission types [2]:

- Commercial Investigational New Drug (IND) applications (for products that are intended to be distributed commercially)
- New Drug Applications (NDAs)
- Abbreviated New Drug Applications (ANDAs)
- Biologics License Applications (BLAs)

All subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect. Master files (MFs), such as Drug Master Files (DMFs), which are considered to be submissions to an IND, NDA, ANDA, or BLA.

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Electronic submission standards will be optional but encouraged for the following categories:

Noncommercial INDs, such as investigator-sponsored INDs and expanded-access INDs Submissions for blood and blood components, including source plasma Submissions for promotional materials for human prescription drug. For exemptions, please see *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry* at www.fda.gov/ectd. Electronic submissions must include only FDA fillable forms (e.g., 1571, 356h) and electronic signatures to enable automated processing of the submission. The most current FDA forms are available at www.fda.gov/AboutFDA/ReportsManualsForms/Forms. Scanned images of FDA forms will not be accepted [3].

Deadlines

NDAs, ANDAs, and BLAs, as of May 5, 2017, must be submitted using the eCTD standard.

INDs and MFs: as of May 5, 2018, must be submitted using the eCTD standard.

Updates to the standard will be announced on the FDA website and published in the *Federal Register*.

Types of Publishing

There are two types of eCTD Publishing activities, which are:

1. Document Level Publishing
2. Submission Level Publishing

Document Level Publishing

Document level publishing means it is the preliminary step in eCTD publishing process, converting the Word document into Acrobat PDF and then creating the Bookmarks and Hyperlinks.

Submission Level Publishing

Submission level Publishing means after completion of pre-publishing activities we need to assign the documents into eCTD publishing tool and then after publishing the submission into output and finally validation.

Methodology

ICH eCTD Specification [4,5]

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.

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 forms and detailed prescribing information (Figure 1).. Please refer to below figure when preparing module 1.

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 1.

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 table 2.

Module 4: Nonclinical study reports This module contains details of nonclinical studies. The name of the folder for module 4 should be m4. 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 3.

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 4.

Figure 1. Module 1 Administrative Information and Prescribing Information

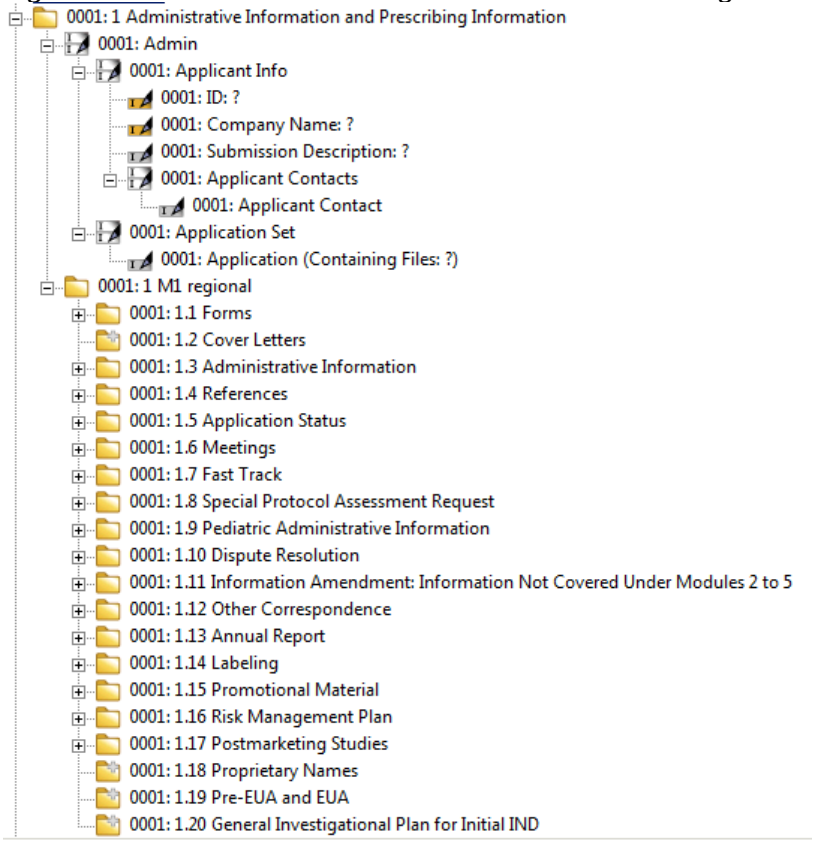


Table 1: Module 2 - Summaries

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*

Table 2: Module 3 - Quality

Section in CTD	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*

Table 3: Nonclinical Study Reports

Section inCTD	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 (ifseparate 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 (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 toxicokineticsevaluations)	*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, includingmaternal function	*42353-pre-postnatal-dev*
4.2.3.5.4	Studies in which the offspring (juvenileanimals) 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*

Table 4: Clinical Study Reports

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-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	*5312-compar-ba-be-stud-rep*

	(BE) Study Reports	
	"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 Listings1	*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. 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 [6]

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. 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” [7].

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 color's 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.

2. 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 adding 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 publishing 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 Control reviewing 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].

3. Quality eCTD Submissions

For an eCTD submission, it is imperative that the company works as a team to develop and submit quality documents refer, that are consistent with the guidance's 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 guidance's related to the submission must be communicated to all individuals contributing to the submission. It may appear that there are a hundred guidance's 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 be successful. 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 guidance's, 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].

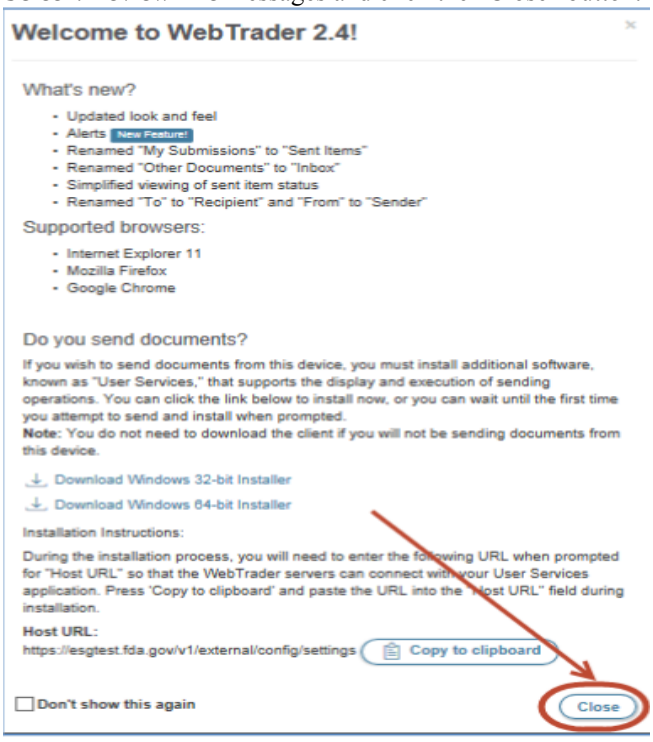
FDA Electronic Submissions Gateway [8-10]

In order to make a single ESG submission via WebTrader, please perform the following steps:

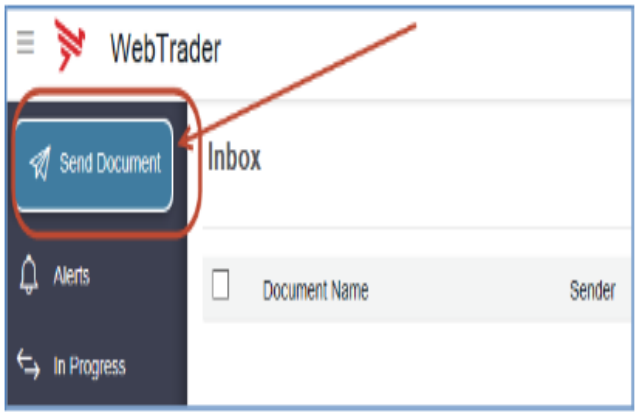
1. Go to https://esgtest.fda.gov/

- Insert your Pre-Production User ID
- Insert Pre-Production Password
- Click the check box next to "I agree to the terms set forth in the Rules of Behaviour. View Rules of Behaviour" and click the "Log in" button

2. When you log into WebTrader you will see the Welcome Screen. Review The messages and click the "Close" button.

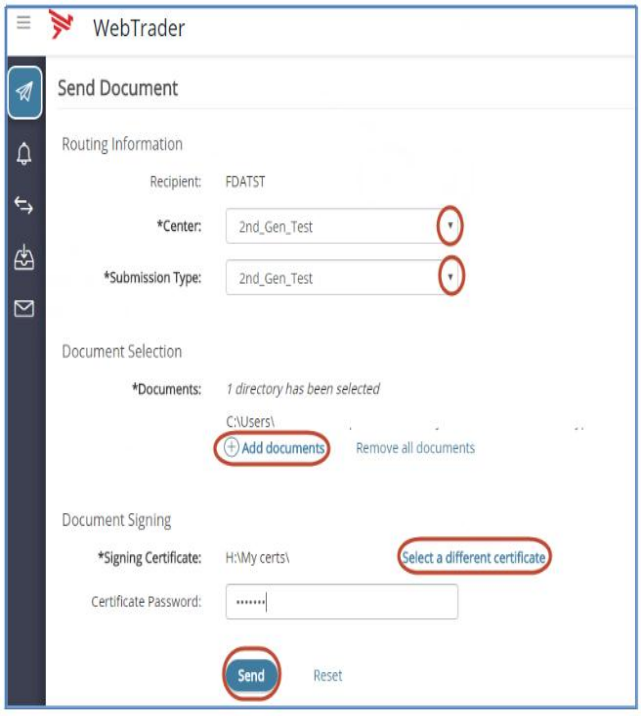


3. To make a submission, click the "Send Document" button in the left-hand window frame:

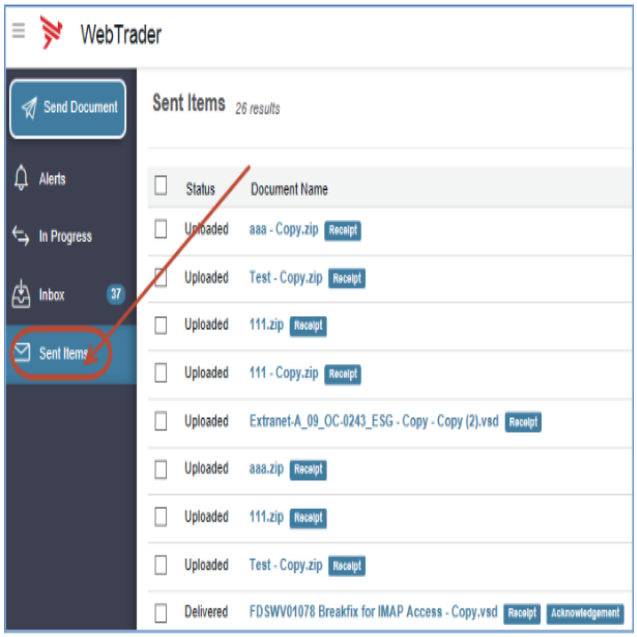


4. From the Send Document page, perform the following steps:

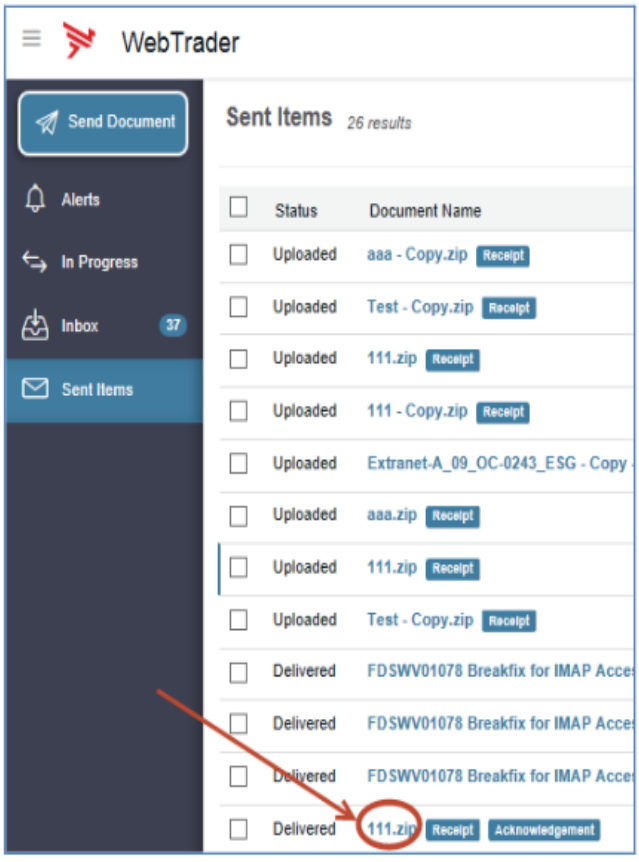
- Select a Centre, by clicking on the down arrow to the right of Centre
- Select a Submission Type, by clicking on the down arrow to the right of Submission Type
- Select the file(s) or folder(s) to be uploaded by clicking on "Add documents"
- Select the signing certificate by clicking on the Signing Certificate link. (You can use your current Pre-Production ESG certificate)
- Insert the signing certificate password to the right of Certificate Password
- Click the "Send" button



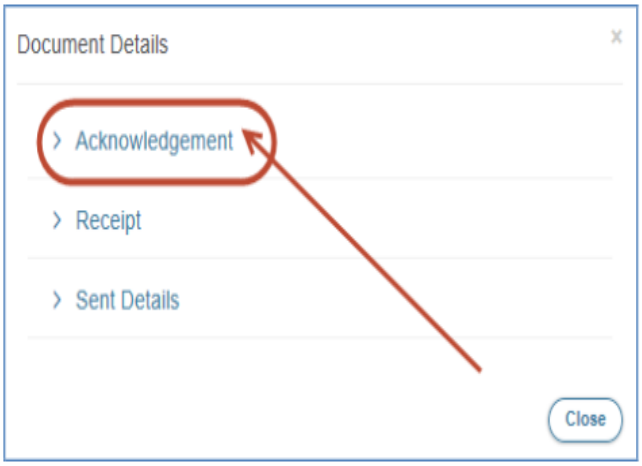
5. To view Submissions, Receipts and Acknowledgements click on "Sent Items" in the left-hand window frame:



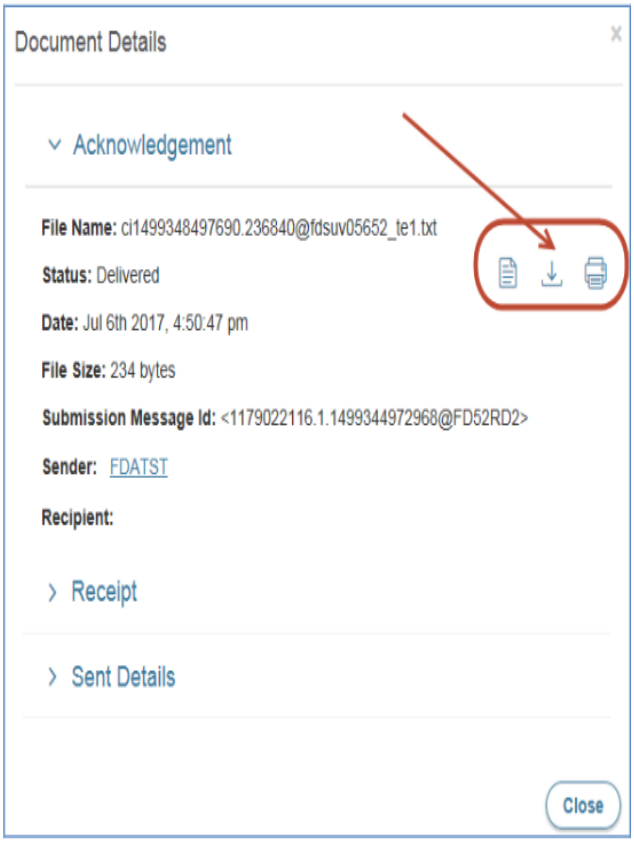
6. Under the "Document Name" column, click on the link for the submitted document. Submissions that have Receipts and Acknowledgements, will have a status of Delivered"



7. After clicking on the link for the Document Name, the Document Details window will appear. In order to see the Submission, Receipt, or Acknowledgement details, click on the link for Acknowledgement, Receipt, or Sent Details:



8. The Document Details will be displayed for the selected item. If the Acknowledgment or Receipt is a text (.txt) file you will be able to view, download, or print. You will need to download non-.txt Acknowledgements to your machine and use appropriate application to view. ESG recommends downloading and locally saving all Acknowledgements and Receipts:



SUMMARY AND CONCLUSION

The submissions process can be traumatic. Whether you are a start - up company filing your first Meeting Request or a major pharmaceutical organization with an NDA for the latest blockbuster, there is a great deal resting on the process and the result.

A good portion of that trauma flows from a perception of loss of control: the submission is delivered, and it seems to enter a black box of FDA review with no clearly predictable outcome. But that sense of control can be regained, and the result made rational and predictable through a careful Quality Assurance process that checks the submission against FDA established criteria and through the use of an internal, self - regulating review process that applies the checklist criteria used by the FDA to the submission development process. In the future, that process is likely to evolve, in part, toward more personalized drugs requiring more targeted submissions; in part, toward a renewed and redirected focus on the submissions review process; and, in part, toward more cost - conscious regulatory processes.

But the importance of a drug regulatory submission and the need to both closely conform to stylistic requirements and to maintain the big picture view of direction, purpose, and eventual label will ream in.

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10. https://www.fda.gov/industry/about-esg/user-guide