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An eCTD Filing for Generic Drug Application in United States of America (USA)

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ABSTRACT:

The major pharmaceutical market in the world is United States. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) has become the obligatory format for the EU, Japan, Canada, Switzerland and Australia, and the recommended format in the US. An electronic CTD (eCTD) was developed in parallel with the CTD. Three ICH regions US, Europe and Japan now accept eCTD filings. The purpose of this article is to survey the eCTD technical requirements in USA and to discuss some of the practicalities involved in writing, compiling and publishing eCTD applications. The eCTD has advantages over the CTD in terms of ease of use, archiving and for life-cycle management of registration information. The eCTD specification defines the folder structure, contents, XML backbone and the Study Tagging File for clinical and nonclinical studies. The design of the eCTD documentation needs to include considerations of document granularity, templates, shell documents and regional differences in filings; for example, the need for an Integrated Summary of Efficacy and Integrated Summary of Safety in the US. Regulatory agencies are moving to accept online filings, but these are currently commonly made using physical media such as CD, DVD or tape. The eCTD file needs to be 'reviewer friendly' by use of bookmarks, hyper linking and tables of contents in individual documents. Many commercial software tools are available for content management, assembly, compilation, publishing, labeling, electronic validation and review. eCTD can be developed using leased or purchased software, specialist contract services, outsourcing from software vendors or using contract research organizations. Introduction of generics with an "Abbreviated New Drug Application" (ANDA) filing with FDA without costly clinical trials and to show similar bioavailability to the brand name drug and manufacture the generic under GMP regulations

KEYWORDS: CTD, eCTD, ICH, ANDA, XML, Regulatory requirement

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INTRODUCTION:

Today the world has become a global village and many companies are in a race to place many new products in the world markets to gain market share and increase earnings. In such a scenario a small delay in gaining market access means huge loss in terms of market share and revenue generated. The pharmaceutical industry is the most highly regulated of all industries that requires a high level of information and data to be submitted to governments and their regulatory authorities before a pharmaceutical product is brought to the market.

Regulatory affairs department is the primary communications link between the company and government agencies such as FDA. Regulatory affairs professionals have expertise in the legal and regulatory environments. Keeping update on regulations is essential in regulatory affairs.

1.1 INTRODUCTION TO REGULATORY AFFAIRS[1-5]

Regulatory affairs (RA), called as government affairs. It is a comparatively new

profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

Regulatory Affairs in the Pharmaceutical industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world."

GOAL OF REGULATORY PROFESSIONAL

- To protect human health
- To ensure safety, efficacy and quality of drugs
- To deliver innovative, breakthrough regulatory strategies for product development and registration

ROLE OF REGULATORY PROFESSIONAL

- Preparation of organized and scientifically valid NDA, ANDA, INDA, MAA, DMF submissions.
- Ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines, regulations and laws.
- Providing expertise and regulatory intelligence in translating regulatory requirements into practical workable plans and advising the companies on regulatory aspects and climate that would affect their proposed activities.

Table 1: World's major Regulatory Authorities[6-14]

COUNTRY	REGULATORY AUTHORITY	WEBSITE
India	Central Drug Standard Control Organization	www.cdsco.nic.in
USA	US Food and Drug Administration (USFDA)	www.fda.gov
Australia	Therapeutic Goods Administration	www.tga.gov.au
China	China Food and Drug Administration (CFDA)	www.sfda.com
Japan	**Japanese Pharmaceuticals and Medical Devices Agency**	www.pmda.go.jp
Europe	European Medicines Agency	www.ema.europe.eu
Brazil	**National Health Surveillance Agency (ANVISA)**	www.anvisa.gov.br
United kingdom	Medicines and Healthcare Products Regulatory Agency	www.mhra.gov.uk
Canada	Health Canada	www.hc-sc.gc.ca

1.2 INTRODUCTION TO GENERIC DRUG[15, 16, 17]

A **generic drug** is a drug defined as "a drug product that is comparable to brand/reference (Patented or licensed) listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use."

Generic drugs are known and labelled with the name of the manufacturer. After Approval of Generic drugs, they are listed in **"Orange Book"** of USFDA.

Generic Drug is widely accepted because before approval to generic drugs in market, only the innovator (patented right holder) molecule is available in market. As drug is innovated, the innovator keeps price of drug very high to get advantage of patent right and to recover the cost of R & D. As patented drug bears high cost, it is very costly to general public. So, USFDA has introduced approval of generic drugs through Hatch-Waxman Act to make high priced patented molecule to be available to general public at affordable cost.

The time it takes a generic drug to appear on the market varies. **In the US, drug patents give protection for twenty years (20) after the date of patent filing.**

Table: 2 ANDA Certifications[18]

TYPE	PATENT CERTIFICATIONS	ANDA FILING
Paragraph I	The drug has not been patented.	If a generic drug manufacturer certifies I & II, then the FDA starts processing the generic ANDA right away
Paragraph II	The patent has already expired.	
Paragraph III	Patent is listed, is valid but the generic wants approval to market the drug once the pertinent patent expires	If a generic drug manufacturer certifies 3, then the FDA starts processing the ANDA, and gives approval when the patent expires
Paragraph IV	The patent is not infringed or is invalid	ANDA filer notifies patent holder within 20 days .Patent holder must sue for infringement within 45 days .If the patent holder sues, FDA must withhold approval for 30 months (one time only). If the patent holder does not sue, FDA may approve ANDA at any time If a court rules that the patent is not infringed or invalid, FDA may proceed after decision. If first generic ANDA files will gets 180 days exclusivity.

1.3 ABBREVIATED NEW DRUG APPLICATION (A.N.D.A) [19, 20]

Generic drug applications are known as "abbreviated" because they are not required to include preclinical (animal) and clinical (human) data to establish drug's safety and effectiveness. Instead of that generic applicants must scientifically demonstrate that their product is bioequivalent as the innovator drug.

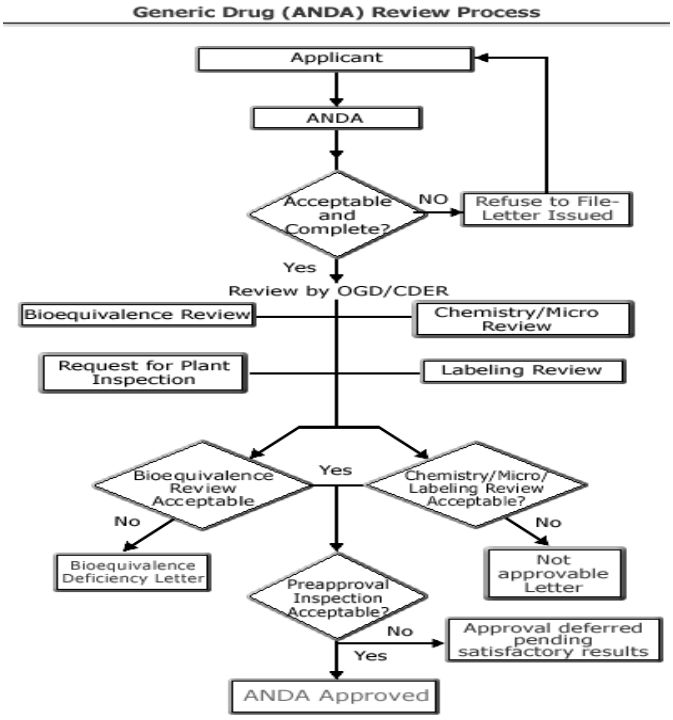

Figure 1: Generic Drug (ANDA) Review process[20]

DIFFERENCE BETWEEN SUBMISSION OF NDA AND ANDA

Table3: Comparison for the innovator (NDA) & generic (ANDA) requirements[21]

NDA requirements	ANDA requirements
1.labelling	1.labelling
2.Pharmacology & toxicology	2.Pharmacology & toxicology
3.CMC	3.CMC
4.Microbiology	4.Microbiology
5.Inspection	5.Inspection
6.Testing	6.Testing
7.Animal studies	7.Bioequivalance
8.Clinical studies	
9.Bioavailability	

1.4 COMMON TECHNICAL DOCUMENT (CTD) [22, 23]

CTD is a set of specification for application dossier for the registration of Medicines and designed to be used by theInternational **Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH M4)**

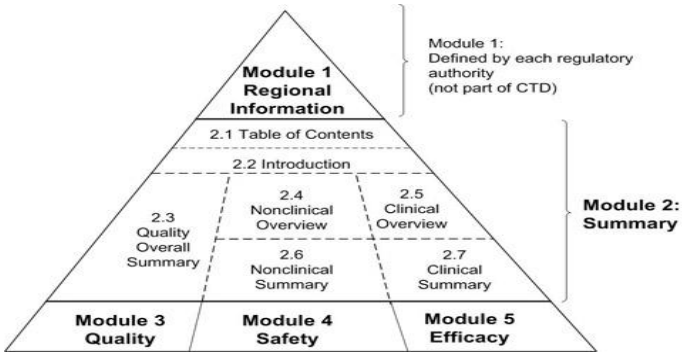

Figure2 CTD Triangle[23]

1.5 ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD) [24, 25]

The eCTD is the electronic version of CTD. **There is no difference between CTD and eCTD in terms of scientific, technical and clinical content.** However, there are regional differences in implementation of eCTD between ICH regions. In theory, eCTD is **vendor and system independent,** in terms of both creation and use. In practice, there have been some reports of issues with interoperability between different eCTD tools, because vendors have not always interpreted the eCTD specifications in the same way.

Role of ICH M2 Expert Working Group(eCTD) and M4 Expert Working Group(CTD)

The goal of eCTD is to enhance the receipt, processing and review of submissions. The eCTD specification has been developed by ICH M2 (Multi-disciplinary Group 2) EWG (Expert Working Group) and maintained by the IWG (Implementation Working Group) in accordance with the ICH process as pertains to the M2 EWG and eCTD change control as it pertains to the eCTD IWG.A version 1.0 XML (eXtensible Markup Language) DTD (Document Type Definition) was completed in February 2002, along with the publication of a version 2.0 eCTD specification. It was finalised in November 2003. Latest eCTD specification version 3.2.2 is available from July 2008.

As of January 2008, the eCTD format is the only acceptable format for electronic submission to USFDA, as all other electronic formats will no longer be acceptable unless a waiver has been granted. Paper submissions are still acceptable but not recommended.

Definition of eCTD is "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 includes all the criteria that will make an electronic submission technically valid. The main focus of the eCTD specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority. The specification for the eCTD is based upon content defined within the CTDICH M4 EWG. **The structure and level of detail specified in the CTD has been used as the basis for defining the eCTD structure and content but where appropriate, additional details have been developed within the eCTD specification ICH M2 EWG.**

Technical answer for eCTD definition is "an XML backbone with associated metadata and checksums, plus a predefined directory structure reflecting the XML nodes and leaves, containing properly granulated and formatted electronic documents". Non-technical answer is "a sort of web page, and a whole set of documents and folders, split up in a particular way, that link together so that the agencies can process your submissions more quickly and easily".

The specification is designed to support high-level functional requirements such as the following:

- Copy and paste document
- Viewing and print of documents
- Annotation of document
- Facilitate the exporting of information to the databases
- Searching within and across all applications
- Navigation throughout eCTD alongwith its subsequent amendments

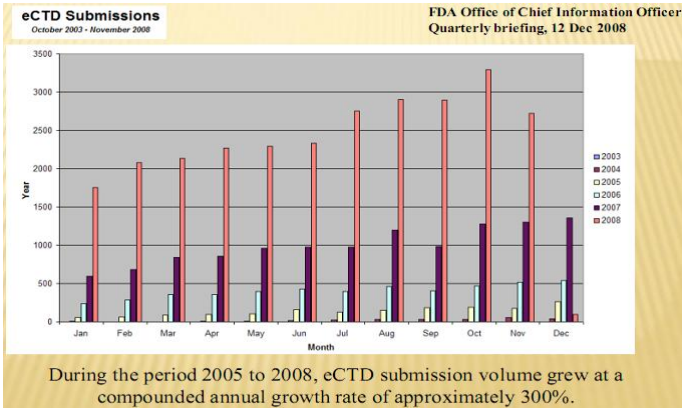

Figure 3: Status of US eCTD submissions (from 2003 to 2008)

CTD LIMITATIONS

- It does not cover the full submission. It includes only modules 2 to 5.
- Does not describe contents of module 1.
- Does not cover details related to amendments to the initial application.

E-CTD ADVANTAGES

- Large reduction in dossier duplication time and expense;
- Large reduction in dossier shipping costs;
- Ease of archiving and distribution;
- Ease of navigation during review, using hyperlinks and bookmarks;
- Facilitation of lifecycle management (keeping track of changes with time);
- Plays a vital role in maintaining information integrity between the pharmaceutical company and the regulatory bodies;
- Reduces time to filing submissions and thereby reduces time-to-market.

EXPERIMENTAL WORK:

ECTD SPECIFICATION

The ICH M2 has defined the specification for the eCTD. The XML eCTD DTD defines the overall structure of the submission. The purpose of the XML backbone is two-fold:

- To manage meta-data for the entire submission and each document within the submission and
- To constitute a comprehensive table of contents and provide corresponding navigation aids.

Meta-data on submission level include information about submitting and receiving organization, manufacturer, publisher, ID and kind of the submission, and related data items. Examples for meta-data on document level are versioning information, language, descriptive information such as document names and checksums.

The 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 names helps (i.e., no random names). Any directory names and file names that are added to the eCTD 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 (Message Digest Algorithm) checksum of the instance. The instance is the starting file for the processing by an XML processor. The intention is to have links from the leaf elements of the instance to the files in the eCTD submission as opposed to creating a single XML document that contains the entire eCTD submission. The instance also contains meta-data at the leaf level.

Checksums:

The eCTD submission should contain checksums for each individual file including a checksum file for the eCTD XML instance. Initially, the MD5 should be used for this purpose. Including a checksum for each individual file provides a number of benefits including:

- The integrity of each file can be verified by comparing the checksum submitted with the file and the computed checksum.
- The checksum can be used to verify that the file has not been altered in the historical archive of the regulatory authority. This is especially useful as the files are migrated from one storage medium to another, as in the case of backup to magnetic tape storage.

Organizing the main submission folder

- The top level of the directory structure will vary by region. The identification of the top-level folder uniquely identifies the application in a region. Submissions should be differentiated by a subfolder named according to the sequence number of the submission in that region.

All documents in the electronic submission should be placed in a main submission folder using a four-digit sequence number for the application with the original submission for an application designated **0000.** Applicant should assign numbers for each submission to the same application with consecutive numbers.

For example, the folder for the 3rd submission to an application, whether it is an amendment, supplement, or general correspondence is numbered 0002. The 4th submission is numbered 0003. See following table 3 for naming convention.

Table 4: Naming convention for submission folder

Example top level folder name	Sequence number	Type of submission
ctd-123456	0000	Original Submission
ctd-123456	0001	First amendment, supplement
ctd-123456	0002	Second amendment, supplement
....		
ctd-123456	Nnnn	Nth amendment, supplement

Figure 4: Naming convention for folder

Applicant should submit the XML backbone as a single file named index.xml, which should be placed in the submission sequence number folder for that submission. In the example shown in Figure, there should be an index.xml file in folder “0000”, folder “0001” and folder “0002”. The MD5 checksum file, indexmd5.txt, should be in each folder with the corresponding index.xml file. The DTD for index.xml should be

in the "util" folder for each submission.

Table 5:Naming convention for file name

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*

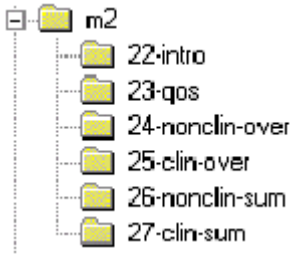

Figure 5: Screenshot representation of the folder structure of module 2

The following case examples show the use of each of the operation attribute values. These examples do not cover all possible situations. Applicant has to consult regulatory authority if have specific questions about the use of the operation attribute. When actually populating the XML instance, use the leaf ID to refer to files.

Case 1 – The first submission of a dossier.

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\structure.pdf	New		structure.pdf (current)

Case 2 – Two submissions

Submission 0000 is the first submission of a dossier. Submission 0001 is a subsequent amendment in which the applicant intends to completely replace the structure.pdf file in submission 0000. The intent is to keep the original structure.pdf for historical purposes but to consider only the contents of the 0001\…\structure2.pdf as relevant to the review. These two submissions could be described as follows:

Module 3 Quality folder

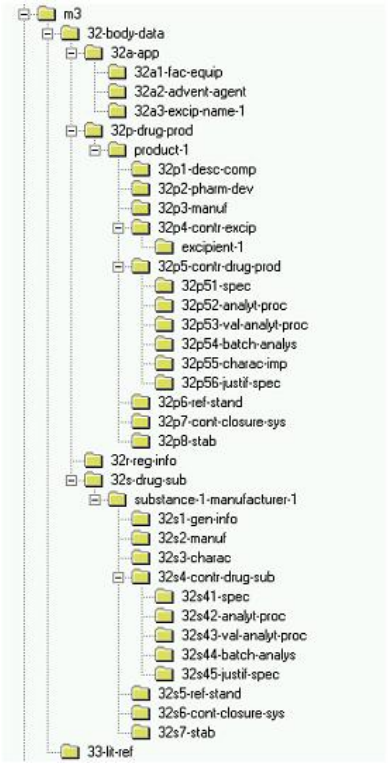

Figure 6: Screenshot representation of the folder structure of module 3

- Submission 0000 is the first submission of the file structure.pdf, and this file is the current version of this file.
- Submission 0001, which is submitted at a later time, is the submission of the file structure2.pdf, which is now current and replaces the file structure.pdf in submission 0000.

There is no requirement to preserve file names during life cycle changes; in fact, logical differences in file names can be helpful during review when both files are open simultaneously for comparative or other purposes.

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\ structure.pdf	New		structure.pdf (current)
0001	0001\…\ structure2.pdf	Replace	0000\…\ structure.pdf	*structure.pdf (replaced)* structure2.pdf (current)

Case 3 - Two submissions

Submission 0000 is the first submission of a dossier. Submission 0001 is an amendment where the applicant intends to add new information to the original structure.pdf file, which was submitted in submission 0000.

The intent is to have the reviewer consider the contents of both files relevant to the submission. These two submissions could be described as follows:

- Submission 0000 is the first submission of the file structure.pdf, and this file is the current version of this file.
- Submission 0001, submitted at a later time, is the submission of the file structure2.pdf, which is the current file but contains information that should be appended to file structure.pdf in submission 0000. Both files should be considered relevant to the review of the dossier.

There is no requirement to preserve file names during life cycle changes; in fact, logical differences in file names can be helpful during review when both files are open simultaneously for comparative or other purposes.

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\ structure.pdf	New		structure.pdf (current)
0001	0001\…\ structure2.pdf	Append	0000\…\ structure.pdf	structure.pdf (current-appended) structure2.pdf (current)

Case 4 - Two submissions

Submission 0000 is the first submission of a dossier. Submission 0001 is an amendment where the applicant intends to delete a file in the previous submission. The intent is to have the reviewer disregard the contents of the original file, possibly because it should not have been submitted with the original dossier. These two submissions could be described as follows:

- Submission 0000 is the first submission of the file structure.pdf and this file is the current version of this file.
- Submission 0001, submitted at a later time, requests that the file structure.pdf in submission 0000 be deleted and no longer considered relevant to the review of the dossier

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\s tructure.pdf	New		structure.pdf (current)
0001		Delete	0000\…\ structure.pdf	structure.pdf (no longer relevant to the review)

DTD Content Model

The content model is hierarchical starting at the “eCTD” and going down to a specific item to be included in the submission.

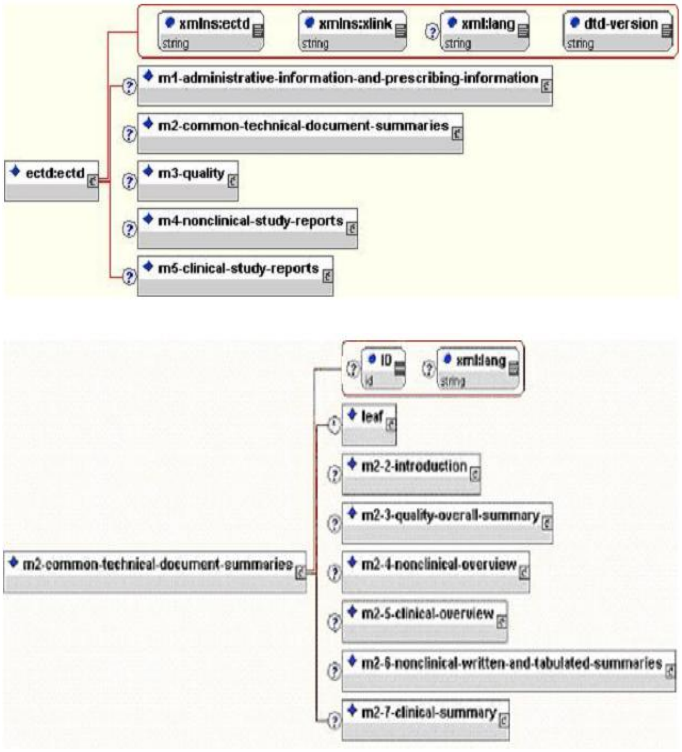

Figure7:Structure of CTD section containing summaries

Once the appropriate element has been selected ,applicant should use the <leaf> element and attributes to specify a file in the submission. See eCTD element/attribute instruction for details.

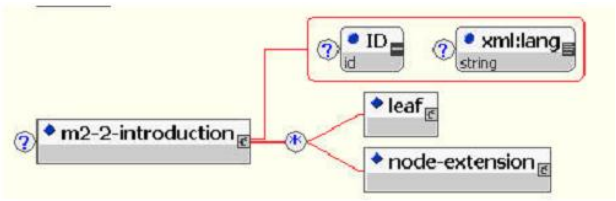

Figure 8: Element in content model

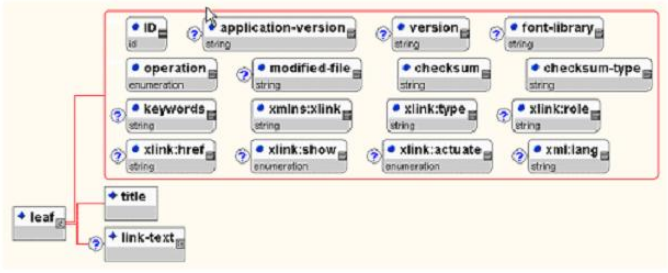

Figure 9: Leaf element and attribute

CONCLUSION:

The technology and business requirements force agency to consider changes in systems, guidelines, process, and so on, to make drug development more efficient and cost effective. Before taking the strategic decision to submit ANDA in eCTD

format, it is essential to review in detail existing working procedures and to identify the changes that are necessary to comply with the eCTD standard. These changes may be either dependent or independent of the format. Independent of format, central co-ordination of involved departments is essential for successful dossier planning. This applies to CTD or eCTD submissions because the move to either has an impact on all functional groups and not just those concerned with regulatory matters. Such changes could lead to resistance to implementation initiatives and so communication to all involved, far ahead of change, is necessary.

Whereas transition to the CTD format did not require any new skills within an organisation, the further move to eCTD is widely seen as requiring new proficiency by both regulatory and information technology staff alike. For eCTD preparation, strong computer skills, including the ability to troubleshoot, are required for regulatory operations and it becomes essential for those concerned with regulation to accept this technological change, so training of existing personnel or the hiring of new staff to ensure that the requisite skills are available should be considered.

Successful transition to eCTD provides following advantages:

- Increased review efficiency
- Decreased risk of refusal to file
- Faster time to market
- Happier stockholders
- Greater employee and management satisfaction
- Lower cost production
- Simultaneous global submission

For effective and successful ANDA filing, applicants have to take following points in to consideration:

- Be sure to reference all files in the XML backbone(s)
- SPL must be in an “SPL” folder
- Include module 1 in all eCTD submissions
- Make sure all application numbers are six digits
- Make sure all sequence numbers are four digits
- Ensure FDA receive what applicant intended
- All XML must use standard components
- PDF contains recognizable text
- Be sure all PDF hyperlinks/bookmarks are correct
- Include TOCs in all PDF documents
- Do not use node extensions
- Use elements and leaf titles correctly
- Verify that all MD5 checksums are correct
- All documents should conform to eCTD granularity.

Preparing an initial eCTD breaks down into four distinct areas:

1. Preparing CTD Modules

The requirement to prepare and submit applications according to the CTD has been around for a number of years. Within eCTD the files which make up an application are linked to one another.

2. Preparing the documents

Each document from CTD modules has to be suitably formatted then converted to PDF, possibly bookmarked and hyperlinked and then checked for compliance with the specifications.

3. Compiling the application

Each document must be given its correct name. The whole folder structure, including most folder names, is defined in the guidance. The various files then have to be examined for any required bookmarking or hyperlinking between files. Next the XML files are prepared. These files act as the index to the application and highlight whether documents are new or replacements during the lifecycle of a product.

4. Publishing the application

The final act is to burn the application to CD o r DVD. After packing of CD, send it to respected FDA address.

Future of eCTD

The FDA is concentrating on a new standard called Regulatory Product Submission (RPS) in collaboration with HL7. The reason for this new initiative from the FDA is to have a single standard for all types of submission they regulate. The eCTD is focused only on human drugs and does not cover devices, veterinary, agriculture and blood-related submissions. The goals of RPS are to have one standard for any type of submission.

There may be a question like, “If eCTD is going away, why am I wasting my time to implement it?” Remember, it took over seven years for the FDA to implement electronic submission (eNDA/eBLA) standards. The e-submissions standard, which started in January 1999, will now be replaced with eCTD in January 2008. The electronic submissions to eCTD transition took over six years. With development of the RPS, is it obvious that it will take at least five to seven years. In the meantime, applicants have to comply with the current standard which is eCTD.

Even if new standards are introduced, it will probably take at least three to six years for those standards to replace eCTD. So, eCTD is here, and it will be there for at least four to five years, or may be even more.

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