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Good eCTD Practices: ways to Avoid Protracting Review Process

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ABSTRACT

In view of digital global agenda, the time has come for Good eCTD Practices. This article holds discussion about the measures to be taken before preparing and while submitting the dossier in eCTD format. The eCTD is an interface between industry and agency for transferring regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission. eCTD is an electronic arrangement with extension of CTD, whose structure is specified by XML (Extensible Markup Language) eCTD DTD (Document Type Definition). While many organizations have delayed their adoption of eCTD format, the USFDA and several other global agencies are pressing forward towards its mandate. Though eCTD specification lists the criteria that will make an electronic submission technically valid, many companies are suffering from delays that occur not due to lack of data but due to technical and other issues of eCTD submission. The eCTD submission requirements definitely pose great challenges to the industry and regulatory agencies. There has to be an investment in information and communication technology as well as development of digital competitiveness among the regulatory professionals within the industry and regulators, alike. The regulatory professionals should know the standards, groundwork, expertise and technology required to submit an electronic submission globally. Due to its cost effectiveness, and because it guarantees a response from the recipient regulatory agency, reducing time to market, the eCTD has become the standard for numerous regulatory agencies around the world.

Keywords: eCTD, Electronic Submission, Study Tagging Files, Granularity, eCTD validation

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INTRODUCTION

Electronic Common Technical Document (eCTD) is a message specification for the transfer of files and metadata from a submitter to a receiver. The content is based on the Common Technical Document (CTD) format. The purpose of electronic Common Technical Document (eCTD) is to present a structured and organized mechanism of electronic submission; the main intent being to become paperless world over. This mechanism must be robust and validated. There are several merits provided for regulators, as well as for applicants, such as the reduction of workload due to less paper. It also aids in physical archiving space. This article discusses the measures to be taken before preparing and during the dossier submission and different considerations to be made while outsourcing eCTD compilation. It also focuses the handling of technical issues in avoiding the rejection of the submission.

Discussion

Figure 1 - The good practices can be understood as preventive actions to be taken before the submission.

Managing the Content[1]

Proper document management practices are essential to the creation, assembly and maintenance of the eCTD. An Electronic Document Management System (EDMS) generally includes such features as check-in/check-out, version control and audit trails and security for all kinds of document file types including word processing documents, XML, images and much more and to establish compliance we should:

- Ensure that EDMS has integrated document process life cycle capability.

Most EDMS systems have built-in functionality for document process lifecycle control and workflow. It's beneficial for submission processes, hence it's included in the content management system.

- Ensuring compliance with 21 CFR (code of federal regulations) part 11.
- Validating all EDMS systems to meet established requirements.
- Creating a mandate for EDMS supported by top-level management.

EDMS projects rarely succeed without backing from all levels of management. If there's no mandate in place, end-users will continue to work outside of the EDMS. Management must support the message that use of the system is not optional but mandatory. Otherwise, lack of co-ordination results in multiple delays.

- Establishing effective policies and procedures upfront.

Compliance cannot be met with technology alone; it also requires effective policies and procedures. Establishing and communicating clear processes and regulations to govern content management systems holds good. These may include:

1. Systems operating procedures
2. Disaster recovery procedures
3. Security and access procedures
4. Operational procedures

- Developing comprehensive strategy for migration.

Migration is often an afterthought for many content management systems. These systems house thousands of critical documents. As these documents progress through their life cycles, many of them have multiple versions, attributes/metadata, electronic signatures and other process information associated with the official record. Developing a comprehensive migration strategy will ensure migration of the total electronic record.

- Avoiding over-customization.

Over-customization is the most common mistake that Life Sciences companies make when it comes to regulatory content management systems. Every company believes their organization is unique and requires custom solutions to be successful. While the organization may in fact, be unique, chances are that EDMS doesn't need to be.

Technical Rejection Avoidance[2]

Regulatory officials have increased their diligence with respect to submission quality and being rejecting eCTD sequences containing significant technical issues. The U.S. FDA has provided written guidance that specifically defines technical eCTD validation criteria. The FDA validation criteria define the impact of a high severity error as "The error is a serious technical error which prevents the processing of the submission and will require resubmission. The submission is considered not received by FDA.

The FDA emphasizes the importance of technical submission quality in their guidance for industry. The agency clearly stipulates that they consider a technically deficient application as "NOT RECEIVED" until

technical deficiencies are resolved and the application is resubmitted. Technical deficiencies may include issues such as:

- Defect in the media (e.g., CD-ROMs)
- Failure to provide an electronically readable 356h or 1571 form for submissions sent through the ESG
- Providing an eCTD submission using a previously submitted sequence number
- Failure to provide the required index.xml and us-regional.xml files
- Presence of a virus
- File format incompatibility

Considerations for avoiding rejections[3]

1. **Always validate prior to submitting to agencies:**

   Validating eCTD prior to submitting to the agency is crucial to quick and efficient drug approval. For eCTD validation, the FDA employs use VALIDATE 2009, which completes a comprehensive error analysis based on their specified criteria. The solution also includes mapping of their current guidance in terms of HIGH, MEDIUM and LOW errors. Using this unique application, one can assign the same criteria in the same manner as the FDA.

2. **Ensure FDA collaboration – use the same software:**

   Avoiding technical rejections can be simple. Just be certain to review all submissions and ensure that they are collaborated with agency reviewers. The FDA uses REVIEW 2009, especially designed for the review of their applications. They evaluate dossier through REVIEW 2009, so the same should be followed.

3. **Establish quality processes and procedures:**

   Establishing quality processes and procedures is essential to successful eCTD implementation. It is important to harmonize the operations and technology to ensure compliance.

4. **QC of the form and cover letter**:

   The most frequent issues seen by the FDA involve inconsistency or errors in between application and submission numbers in the US regional XML backbone, application form and cover letter. Final quality checks of these components for correctness and consistency should be included.

Document Templates[4]

Document templates help promoting compliance with regulations concerning granularity, formatting requirements and others. Templates provide direction for the authoring community so they don't have to consult standards or become MS Word experts before doing the work they need to do.

Even if organization is not ready to produce eCTDs, creating eCTD-ready documents will provide a major benefit and cost savings down the road. Every Life Sciences organization should.

- Decide whether to build or Buy – If you don't already have templates mapping to eCTD granularity is not available; consider buying a set of templates rather than creating your own. There are several packages available at different price points and levels of sophistication.
- Control and Manage Templates – once the templates are obtained, make certain that they're available to authors in a standard location, preferably your EDMS. Control all changes to templates by enforcing a review and approval process.
- Train Authors –Authors need to be trained in using templates and recognize why they are important. Once they understand the need for submissions to follow guidelines for submission, they'll be less likely to modify their documents in a noncompliant manner. This will avoid costly, time-consuming re-work by regulatory operations or outsourced publishing partners.

Study Tagging File (STF)[5]

Study Tagging Files, according to the ICH definition are "an XML instance controlled by the ICH STF Document Type Definition (DTD)." In order to efficiently process and review applications, information is needed on each document including the document title, subject matter, relationship to other documents, revision information, the location of the document and information on the submission that included the document. The eCTD backbone files do not contain enough information of the subject matter of study reports and their related files. This additional information is provided in the study tagging files (STFs) and is important because it provides information, which makes it easier to identify documents and to make the submission easier to navigate through for reviewers. STFs are required by the United States, are not required in Europe and are not allowed in Japan. While study tagging files things to be considered are as follows:

Each study must have a Study Tagging File, even if it only includes a single document. Making the mistake of thinking that the STF is unimportant for a single-document study is wrong—the information is required to organize the document for viewing in the FDA's viewer. It's important to assign an accurate study number and meaningful, concise study title to each study, including nonclinical studies.

Study metadata is also used to organized studies. Metadata depends on the type of study (such as Single-Dose Toxicology) and may include species, route of administration, duration, control type or no metadata at all. QC of metadata carefully is necessary, as eCTD contains no methodology for updating incorrect metadata (such as a wrong species).

Each document in a study must be assigned a file tag identifying its contents. Understanding the file tags and their usage is important.

For non-U.S. submissions (especially EU) understand whether the used publishing tool will automatically remove the STF, and if EU submissions are published first, the process occurs in reverse.

eCTD Granularity Considerations[6]

Granularity can refer to the level of hierarchy of the folders and files in the eCTD directory tree or the smallest unit of detail within the eCTD tree structure. Granularity specifically impacts the following areas of submission management:

Submission Maintenance

Because organization can only replace entire documents in the eCTD, not sections or pages, submission's initial granularity choices affect updates that will be made over the application life cycle.

Submission Review –

Choosing a lower level of granularity allows agency reviewers to locate specific information. However, in some cases, it may be easier for them to review a single document rather than a large volume of small documents.

Best practices with respect to eCTD granularity include:

Knowing the levels of granularity that the authorities specify and where flexibility is available to the sponsor. The main decisions are to be made around the QOS (Quality Overall Summary) in Module 2, certain portions of Module 3 and the construction of study reports in Modules 4 and 5.

Understand the advantages and disadvantages of increased granularity. Authoring in smaller sections streamlines future submission maintenance. However, it can also complicate review, approval and assembly processes. Considering how likely a document may be required to change over time before making your decisions.

Ensuring that electronic document management system supports desired level of granularity is important. EDMS should allow classifying documents at the desired levels and providing templates to assist the authors.

Reviewing the eCTD[7,8,9]

Missing documents and broken links are just a few of the things that can make your eCTD submission non-reviewable. To ensure submission success, every detail, from confirming its technical accuracy to verifying that the contents are exactly where health authority needs to be and ensure that each link works without fail.

Things that should be considered:

- **Reviewing & clarifying current guidance**

Regulations are not static entities; they change over time. Before first submission is reviewed, you should have a clear understanding of current procedures and develop a practical approach for your organization to support this guidance.

- **Creating a review checklist**

Review process should be thorough and repeatable. Checklist outlining review criteria and assign responsibilities should be created and followed.

- **Defining the hyper linking practices**

A major challenge of electronic submissions is incorrect hyper linking. As regular file maintenance occurs over time, some of the files may be deleted or replaced, resulting in broken hyperlinks that point to out-of-date files. When reviewing dossiers, checking that all linking is active and working properly is must.

- **Creating PDF's from electronic sources**

In most cases, regulatory authorities would prefer not to receive scanned documents. Rather than scanned input, PDFs should be generated from the electronic native documents wherever possible. The ability to search in and copy text from these documents is critical to agency reviewers. If there are handwritten signatures in the documents, consider practices that will allow these signatures to be included in source documents without scanning.

- **Using a fillable 356h (or other application) form**

The FDA has a strong preference for fillable forms. Although the agency has not mandated the use of these forms, they have noted that the advantage of using the gateway for submission diminishes considerably if fillable forms are not used.

- **Establishing healthy communication with the health authority early**

Establishing clear communication with the health authority is an important step in delivering "reviewable" submissions. In the U.S., communication begins with the FDA Office of Business Informatics (OBI) – Division of Regulatory Review Support, who will provide assistance to industry in support of the submission review process.

eCTD VALIDATION[10]

It's necessary to validate the dossier not only at different stages of the life cycle, but most importantly, before submission, to verify compliance with current regulatory guidance.

- **Understand the validation criteria of the health authority**

Health Authorities in Canada, Europe and the U.S. each have their own set of eCTD validation criteria published on their websites. Understanding validation criteria for your market makes it easier to detect errors considered critical by the Health Authority to which it is being submitted.

- **Understand the capabilities of the tools used**

Publishing tool may detect some errors; chances are there that it will not detect all errors considered important by every Health Authority. If there is no 100% critical error coverage in the tool suite, manual checks should be performed, which are time consuming and labor intensive there is no escape.

- **Avoiding manual edit of the xml**

It's easy to get your publishing tool "out of sync" with the submission while editing eCTD XML code manually. There are many tools on the market designed to check the structural integrity of your XML. Be sure to use an automated tool to avoid unnecessary technical errors.

- **Correcting of all errors before delivering the submission**

Many companies do not correct errors because they think those errors aren't critical. But by correcting all errors prior to submission, certifies that not a single critical error is missed. A good way to summarize and categorize errors is to run a validation tool prior to the submission. Validate tool should provide not only error checking, but also robust reporting that allows to summarize and systematically correct all errors.

Submission Outsourcing Best Practices[11]

Organizations considering the move to eCTD have to decide whether to prepare submissions in-house with a publishing tool or outsource to a publishing partner. The costs and risks associated with acquiring software, developing processes, training staff and actually performing eCTD publishing may not be justified based on expected submission volume. In this case, organization should contract with a partner company to produce and submit eCTDs.

Some keys to keep in mind while choosing a partner:

- Experience of the partner in target market(s).

Experience of the partner can be judged by no of applications and sequences they have submitted, and what are the application types (IND-Investigational New Drug, NDA-New Drug Application, BLA-Biologic License Application, DMF-Drug Master File, ANDA-Abbreviated New Drug Application) they have handled.

- Sharing of the work between organization and partner.
- Quality control standards used by the partner organization.

Evaluate quality control parameters, checklists for documents and for the submission.

- Validation of the eCTD by the partner.

Ideally, the partner's validation process should guarantee 100% of the validation checks for your submission market. Should discuss what happens if a submission is rejected due to technical errors.

- QC of the submission after the preparation.
- Partner as a trusted adviser.

Partner should advise on best practices answer your questions and guard against common issues encountered with the eCTD.

CONCLUSION

To establish a process by which eCTD submission can be considered on a routine basis in future. There needs to be a system to produce xml backbone. Source documents and data need to be submitted should be ready and compliant with requirements and certain points that may ascertain to be in compliance should be considered like setting standards in the beginning, choosing meaningful file names, keeping similar studies together, clear communication with reviewers, choosing an appropriate level of granularity, applying helpful hyperlinks, considering future life cycle management etc. Sponsors should understand, be aware and well prepared on how agencies use the components of an eCTD for review**.**

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