

## **Preparing for the eCTD**

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## **INTRODUCTION**

The Electronic Common Technical Document (eCTD) is an initiative that was introduced to industry by the International Conference on Harmonization (ICH). The potential that is envisioned by most companies as they seek to implement the eCTD is two-fold. First, most organizations see value in electronic processes and the benefits in the manipulation, review and distribution of electronic documents and supporting data. Second, for organizations that are faced with the challenges of submitting to multiple health authorities, the eCTD offers a way to reuse a core set of information across regions. The combined benefits of electronic submissions and minimal rework across regions offers a glimpse into the future of regulatory submissions. This future includes a very different submission compilation process that includes new deliverables. These new deliverables require a different perspective, potentially new skill sets and the use of innovative technologies. This paper will provide a framework for developing eCTD capabilities using a methodology that looks at the submission development process as an organizational rather than a departmental initiative.

## **eCTD COMPONENTS**

The current specification (V. 3.0, dated October 8, 2002), describes the eCTD in terms of three basic components: the eCTD backbone, content files (submitted in Portable Document Format or PDF), and a clearly defined folder structure with a specific file naming scheme. In addition, in the U.S., data files should still be submitted in SAS Transport format.

The eCTD backbone is an XML file that contains metadata about the submission and each of the files comprising it. Agency review tools utilize this metadata for navigation and presentation of the submission components. The eCTD Viewer System (EVS) review tool developed by the Food and Drug Administration (FDA) uses the backbone file to present information in the initial submission and also to show relationships between the original submission and subsequent amendments or supplements. The management of this information and relationships between content files throughout the chronology of submissions is referred to as submission lifecycle management.

While CTD guidances outline specific content topics, the eCTD specification clearly describes the organization of content files into a folder structure with file naming standards. A notable difference from other electronic submissions specifications or guidances is the granularity of files being submitted. Granularity refers to the degree to which files are broken down into individual components. The eCTD specification requires files that were previously compiled into larger components, be broken down into smaller "chunks" of information. Each component contains content but also requires associated metadata that is stored in the backbone file. Higher granularity means more components. Because each of these components also requires submission of metadata in the backbone file, many organizations have begun struggling through the realities of submission lifecycle management. Managing all of the components in the context of the submission can be a daunting task. Submitting the correct components with the correct metadata makes the task much more complex.

Members of the ICH eCTD working group developed the study-tagging file. This concept breaks the traditional ICH E3 formatted Clinical Study Report into small granules and provides an associated XML file containing metadata about each of the granules. During the development of the eCTD specification, the need for further definition of clinical and non-clinical studies was identified. A methodology that would support submitting study reports as multiple files was developed. This methodology is facilitated through the use of a study-tagging file. A study-tagging file enables sponsors to organize and manage their study reports in a highly granular way, while having minimal impact on the implementation of the

eCTD backbone. It also enables sponsors to finalize portions of the submission earlier in the process because they are tracked and managed as separate components. Reviewers and sponsors can benefit from the inclusion of additional metadata. However, sponsors will be required to manage the lifecycle of many more submission components.

## **A PROCESS-CENTRIC APPROACH**

Some organizations immediately turn to technology to address the tall order submission lifecycle management. However, it is important to consider technology as part of the larger solution. A tool is required to automate manual processes and present required information to the user. The tool should not define an organization's processes. In fact, because many eCTD tools are strictly focused on the final publishing process, they in fact limit the return on investment that a sponsor can expect. To maximize your organization's eCTD capabilities and investments in technology, it is imperative that solid cross-functional processes are developed based on the requirements for submission deliverables.

This concept usually requires a significant shift in perspective for organizations that have developed paper submission processes. In the paper world, documents are finalized and passed to the publishing group for compilation and copy production. As previously mentioned, a submission-ready component for the eCTD includes a content file and associated metadata. This metadata must go through similar quality checks and reviews to ensure its accuracy. The backbone where all of this information is stored must be created and if it is not the original application, relationships between current content and previously submitted content must be created. In most cases, this data was not previously tracked in existing systems so an "owner" of this information must be identified and a process for developing and tracking the information must be created. This approach will enable the organization to adapt to changing specifications and choose the best technology solutions that will support the process

## **CHANGE MANAGEMENT AND A CAPABILITIES ASSESSMENT**

One of the biggest challenges to implementing an eCTD strategy is effectively managing change within the organization. It is important to start an eCTD initiative by assessing the current capabilities of the organization. An assessment of this nature should include all aspects of an organization's assets, including current skill sets, organizational experience with electronic submissions (specifically the CTD and eCTD), current technologies, and standard operating procedures.

Skill sets required to create an eCTD submission should be assessed against existing skill sets within the organization. Most companies that have developed paper submission processes have developed competencies in scanning, quality control and production of paper volumes. Some of these skills are transferable to the electronic processes but new skills will be required. For example, a resource proficient in the use of xml editing tools will be invaluable when addressing last minute modifications of the backbone file.

It is also important to gain some insight into the organization's experience, knowledge and understanding of the eCTD specifications. Many companies have been involved in pilot programs with regulatory agencies and some organizations are actively participating in expert working groups within the ICH structure. Knowledge gained from such activities will help the organization map processes to the eCTD requirements. Most likely, the results of this assessment will identify a need for broader eCTD training across contributing departments. Traditional paper submission processes are linear in nature and push

submission compilation to the end of the process, usually within a Regulatory Operations function. The granularity specified by the eCTD exposes an opportunity to shift some of these activities upstream to contributing departments. This allows content owners to produce "submission-ready" documents and smooth the resource spike that typically results within the operations group during the final weeks prior to submission.

An assessment of current technologies is also important. This assessment should not only look at current document management and publishing capabilities but should also identify capabilities of contributing departments to create eCTD components. Tools such as authoring and data capture technologies should be included in the analysis. For example, all EDC (electronic data capture) solutions are not created equal. The output from some EDC systems requires rework to generate compliant electronic submission components. These rework scenarios should be captured in the assessment phase to determine how best to improve the overall process.

It is also important to understand where technology gaps exist. Does the organization have access to an XML editor? Is there at least one individual with an understanding of both XML and the eCTD guidance? Is a document management system in place? All are important questions in understanding the scale of implementation activities required to support eCTD production.

Finally, standard operating procedures should be reviewed. Typical SOPs are generated within a department and may reference related SOPs from other functional areas but are usually not tightly integrated. A review of SOPs across R&D will quickly pinpoint areas where efforts are duplicated across the organization and will also provide information about transitions that will be required for paper processes. Cross-functional SOPs that are designed around eCTD deliverables will provide efficiencies throughout the organization. As data and documents flow between departments, efficiencies will be compounded as each rework scenario dissolves.

## **DEVELOPING A STRATEGY**

Once you have a clear understanding of the organization's strengths and weaknesses, you can begin to develop a strategy to acquire eCTD capabilities. It is important to note that this may require technology changes, modified or new SOPs, additional training on tools, processes and the eCTD specification, or a combination of the three.

The task of grasping the nuances of the specification and incorporating them into a practical approach across the organization may seem daunting. However, your strategy may include outside resources to address the new requirements as the organization gains experience. An outsourcing strategy that is integrated with technology acquisition allows the company to gain the benefit of outside expertise while developing internal capabilities. This approach is becoming increasingly common in the industry because it gives companies the flexibility to gain experience while minimizing the risk of failure.

The strategy should include support for original applications as well as maintenance submissions. Good lifecycle management will dictate the identification and tracking of additional metadata. Keep in mind that the eCTD submission will be an evolving application. It is not the static submission that exists in the current paper submission world. As updates or amendments are generated, their relationship to prior submissions must be established through the metadata. This also places an additional emphasis on the importance of good document management.

Your strategy cannot be developed in a vacuum. Each day your pipeline is changing and “in-process” submission dates are fluctuating. Consider rolling out your eCTD strategy on a project-by-project basis. Choose the project with consideration for team membership and willingness to accept change, pipeline activities, amount of legacy documentation and degree of risk based on the importance of the submission. If some submission components have already been drafted in another format, you will need to incorporate a conversion strategy into your plan. If you can provide authoring templates to a team before most of the documents are drafted, you can reduce the amount of rework or conversion that is necessary.

You should also consider implementing the strategy over a period of time. This phased approach requires you to prioritize essential activities but also enables time to adapt incrementally as you gain experience and develop internal expertise.

It is also important to communicate progress to the organization. Planned communications of project milestones, successes and failures help to manage expectations. This is particularly important in regard to interactions with senior management. Many high-level R&D executives believe in the benefits of the CTD and the eCTD but do not have an appreciation for the amount of work required to support a successful transition.

#### **AGENCY CAPABILITIES**

It is important to realize that as you face the challenges of creating an eCTD capability across your organization, regulatory authorities around the world are tackling the same issues from the receipt and review perspective. Some authorities such as the U.S. Food and Drug Administration have begun to develop the infrastructure to accept eCTD applications and are testing tools that will facilitate global reviews. However, many are still struggling with challenges of the transition from paper to electronic. The agencies face the same issues of developing new processes, acquiring new technologies and training personnel on new tools, processes and deliverables. As their plans progress, differing implementation schedules around the world will require flexibility on the sponsor’s side to support various submission scenarios including paper CTDs until agencies can develop appropriate infrastructures to support receipt and review of eCTDs. In addition, the sponsor’s shifting pipeline combined with the authorities’ evolving implementation schedules will certainly result in some very interesting scenarios.

#### **CONCLUSION**

The implementation of the eCTD across an R&D organization requires cross-functional procedures, which in turn, will require cross-functional roles and responsibilities. Because these are emerging roles, new skill sets will most likely be required. As vendors develop tools to support the process and agencies announce different implementation schedules, organizations will have to support transitional models for electronic submissions. All of these factors place a huge emphasis on training and the need to move the organization toward a viable submission strategy. Companies that embrace the concepts will inevitably experience success in developing and maintaining eCTD capabilities that will offer efficiencies across the organization.