

# **Evaluating the Electronic Submissions Challenge in the Pharma and Biotech Industries**

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## **1 INTRODUCTION AND OVERVIEW**

eCTD, XML, SPL, electronic signatures, 21 CFR Part 11, electronic gateway...these are the buzz words of the 21<sup>st</sup> century for pharmaceutical and biotechnology drug development. Today, these terms represent a challenge to each and every company in the pharmaceutical industry...from R&D to contract manufacturing to CROs and to regulatory agencies worldwide. Why? An organization must decide WHEN, not IF, they will integrate these new technologies and guidelines into their internal business processes, and if so, HOW.

Before an organization determines if they will integrate new technologies and guidelines into their existing internal business processes, they must understand the overall landscape of what will be impacted. For example, if an organization develops their own drug compounds, the process of taking those compounds to market is expensive (approximately \$800 million)<sup>1</sup> and time-consuming (minimum 12 years).<sup>2</sup> Considering that the documentation paper trail during this cycle can be upwards of 500,000 pieces of paper<sup>1</sup>, additional costs of managing volumes of paper have just been added to the already costly development process.

If one single sponsor can generate 500,000 plus pieces of paper for a single compound, imagine the volume of paper received by regulatory agencies worldwide throughout the lifecycles of all successful compounds. The numbers are exponential.

How do electronic submissions address and solve the problem of building a mountain of paper? Electronic submissions transform the documentation process of the drug development lifecycle into a virtual paper trail by significantly reducing the volume of paper to manage.

## **2 EVALUATION OF EXISTING BUSINESS PROCESSES**

The key concept of electronic submissions is to “transform” the documentation process. The transformation impacts HOW the authors will prepare DMFs, INDs, NDAs, MAAs, etc., as well as the overall interaction between the sponsor and all major partners in the drug development process. If a sponsor decides to submit their applications electronically, the requirements of the document deliverables from their vendors will need to be based on the electronic submission guidelines.

Where should a sponsor start in evaluating whether or not to submit their applications electronically? Perhaps the best place to begin is to understand that transformation means change...and change is usually not easy to implement and manage. A thorough examination of existing document authoring processes and author's preferences will help determine the most effective strategy for the transformation process.

If a sponsor has already implemented the International Conference on Harmonisation (ICH) common technical document (CTD) format, 50% of the transformation process has occurred. If

the CTD format has not been implemented, this is truly the first step. Understanding and implementing the CTD format will help the document authors become familiar with the standardized format. The CTD format introduces concepts such as modules, summaries, sections, and document granularity (i.e. whether a CTD section will be a single document or multiple CTD sections will be combined into a single document). Initially, working with the CTD format is challenging. However, once the CTD format concept is understood and experience is gained, most authors (and regulatory reviewers) prefer the CTD format and the advantages it offers.

The CTD format offers many benefits over the original traditional formats. Using the traditional formats, authors could only work on documents in consecutive order. Therefore, if two authors needed to work on the same document, it was virtually impossible for both to work on the document electronically. CTD allows multiple authors to work on the same module (i.e. Module 3, Quality) simultaneously, thus reducing the document preparation time.

The traditional format required consecutive pagination from the beginning of the application to the end, which created a significant amount of manual page stamping and added time to the back-end of a project...compressing the amount of processing time. CTD allows for pagination with each section to begin on page 1. Again, this improves the efficiency of document preparation time and minimizes the amount of back-end project work.

Using the traditional format, amendments, annual reports, etc., sometimes required information to be resubmitted because of a small change. The document granularity of the CTD accommodates amendments, annual reports, etc., to contain single sections for that same small change and eliminates the need to resubmit unchanged data.

The next step in evaluating the existing business process is to understand version control throughout the document preparation process. Version control can either be very complex or relatively simple. Determining how version control will be handled is a discussion between the document authors, QA, Regulatory Affairs, and support staff (this could encompass word processing, compilation, shipping, etc.). A differentiation should be made between major and minor versions, what constitutes a necessary revision versus word-smith, and when a document is final. Version control can also be a key component in determining submission timelines by identifying when major drafts will be available for review.

The third step is to evaluate the document process flow and identify potential bottlenecks and process inefficiencies. The CTD format and version-control standards will add efficiencies to the document preparation process, but reviews and compilation activities are usually problem areas. If the document preparation process is linear, consider activities that could be conducted in parallel. If the document preparation process is already staggered or activities are parallel, an evaluation of the value added by the individual activities should be considered.

### **3 EVALUATION OF THE ELECTRONIC SUBMISSIONS CHALLENGE**

After the previous steps have been considered and completed, an organization is ready to analyze, evaluate, and decide how to implement an electronic-submission process. This decision

is challenging because of the numerous factors that must be considered. The primary factors to evaluate are impact on existing business processes and personnel, cost, and future direction of the industry.

For most organizations, the initial conversation for the electronic-submissions challenge should start with an assessment of the overall impact e-submissions will have on the existing business processes and available personnel. When most people think of e-submissions, and specifically the electronic common technical document (eCTD), they believe that e-submissions are the responsibility of Information Technology (IT) Departments or Regulatory Affairs Departments. In reality, e-submissions are the responsibility of everyone in the organization involved in preparing regulatory submissions. Why? Because e-submissions will change how authors prepare documents, how reviewers review documents, and how support staff compile the final documents into a complete submission.

How will the eCTD change the way authors prepare documents? Authors will need to approach document preparation based on the CTD granularity requirements. When laying out the project plan and project timeline, consideration should be given to the appropriate level of document granularity. Some would argue that this is too early in the process to determine the level of document granularity. When considering document granularity, keep in mind that if the granularity is not low enough, additional work may be required to split the document into more granularity later in the process. Depending on how late in the process this would occur, an unnecessary critical-path issue might be created that could impact the overall submission timeline.

Another issue for the authors to consider is how to handle cross-references. In electronic submissions, cross-references are crucial for proper navigation within the submission. Authors need to determine what cross-references will be either intra-document or inter-document. There are features in Microsoft Word the authors may use to facilitate cross-referencing within the same document, as well as using heading styles and format styles to create bookmarks. Another aspect of cross-referencing is the Table of Contents (TOC) within a specific document. If the TOC feature in Microsoft Word is used by the authors, the page numbers will update automatically as the document grows.

How will the eCTD change the way reviewers review documents? Rather than reviewing volumes and volumes of paper, reviewers will review the submission electronically. As part of the electronic review, reviewers will check the navigation within the submission (are the bookmarks and links taking the reviewer to the correct destination) as well as the technical content. Within either the publishing group or the regulatory affairs group, a review will also be conducted to guarantee the electronic submission is in compliance with the latest regulatory guidelines.

How will the eCTD change the way submissions are compiled? This is the area that is most impacted by a transition to electronic submissions. For years, support groups have compiled submissions by organizing and managing thousands of pages of paper. Nonclinical and clinical study reports had to be hand-stamped to maintain consecutive pagination within an application. Tab identifiers had to be prepared and inserted manually into the appropriate location. Multiple

copies of the documents had to be made, checked, and assembled. If a mistake was made or new information needed to be included...hours of rework were necessary to make the change.

Electronic submissions require the organization and management of multiple electronic files. This shift represents a significant transition for an organization's office practices, as well as their IT needs. The organization must evaluate if they have the right personnel in place to make this transition. This part of the evaluation process involves two of the primary factors: personnel and cost.

#### **4 EVALUATION OF ESubmission SOLUTIONS**

If an organization determines they want to proceed with an electronic submission solution, an evaluation of existing personnel and the available options for preparing and compiling electronic submissions is the next step. This evaluation process should consider an in-house solution, outsourcing the electronic publishing, or a combination of the two.

When considering an in-house solution, an organization must evaluate the costs of software, hardware, validation, training, and maintaining qualified personnel. An estimate of the least-expensive in-house solution to produce eCTD submissions is approximately \$300,000...and that doesn't include personnel costs. An estimate of the most-expensive in-house solution could easily be seven figures...depending on the size and complexity of the organization. These figures represent the initial investment and do not include any personnel costs or the ongoing costs associated with maintaining the electronic publishing system. Industry estimates that turnover of publishing personnel is 50%. The turnover percentage alone represents a significant reinvestment for an organization.

When evaluating outsourcing as an electronic publishing solution, an organization must evaluate the cost and value-received for the service, the integration with internal processes, and the desire to create a long-term relationship with an outside vendor, because once an eCTD, always an eCTD.

The third possible solution to producing electronic submissions is implementing a combination of an in-house solution and an outside vendor. Under this scenario, an organization may develop their own internal document standards and processes to facilitate the authoring and review cycle, but choose to use an outside vendor for the actual "publishing" and compilation of the electronic submission. The vendor, in this case, would be responsible for converting the authored documents into the proper electronic format, adding the necessary navigation aids, and compiling the submission electronically.

The final area of consideration is the future direction of the pharmaceutical industry and regulatory submissions. In many respects, this area is the most challenging because of the uncertainty surrounding what government agencies will do in the future. The most recent activity indicates that global regulatory agencies are moving towards requiring electronic submissions within the next 3-5 years<sup>3</sup>. For example,

- FDA has announced that all electronic submissions must be in eCTD format effective January 1, 2008.
- Europe has indicated that after December 31, 2009, ALL regulatory submissions must be electronic.
- Japan “officially recommended” using the eCTD in April 2005, although the official submission is still paper.
- Canada will accept a complete eCTD submission accompanied by a paper copy of Modules 1 and 2.

## **5 CONCLUSION**

So for the pharmaceutical industry, the question remains on HOW to approach the challenge of implementing an electronic submissions solution. The answer is dependent on how far along in the document transformation process an organization is. If an organization is just starting this journey, electronic submissions pose a difficult challenge because of the enormity of what lies ahead. If an organization is already progressing along the path to implementing an electronic submissions solution, the challenge isn't as difficult. One thing is for certain, global regulatory agencies and the healthcare industry as a whole view electronic submissions and electronic records as the future direction of the industry. **NOW** is the time to let go of paper and embrace the future.

## **6 REFERENCES**

- 1 Kyberpass Corporation White Paper: Electronic Submissions in Compliance with Regulatory Requirements for the Global Pharmaceutical Industry-Bridging the Gap between Document Management and High Security 2004
- 2 Goel, Aatish, and Sundararajan, Murali Krishnan, “Managing Electronic Submissions through eCTD with Strategic Partners”.
- 3 FDAnews Management Report “CDER’s Electronic Requirement for eCTD”, 2007