

Outsourcing: A Rapid, Cost-Effective Option for Electronic Submissions

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1 - Introduction

Pharmaceutical and biotech sponsor organizations are in increasing numbers making the switch from paper to electronic format for their marketing applications to FDA. The decision to adopt the electronic Common Technical Document (eCTD) submission format is a strategic one, offering the sponsor these important benefits:

1. a greatly enhanced ability to efficiently organize, prepare, and manage submission content,
2. the opportunity for streamlined interactions with agency reviewers, and
3. a potentially more efficient and thorough agency review.

Barriers to adoption typically include:

1. costs (initial capital: \$200K- \$300K and annual expense: \$100 - \$200K) of building, validating and operating an electronic publishing system,
2. effort and time to learn and understand the regulatory requirements and to develop the organizational competency to efficiently produce compliant eCTD submissions.

Given the current difficult economic environment, sponsors, especially those with modest submission volumes, should give strong consideration to outsourcing as an option that can enable the strategic benefits of eCTD while significantly reducing the barriers.

2 - eCTD Trends, Facts and Considerations

> US Submission Trends and Facts

Since FDA first established the capability to receive and process submissions in eCTD format, there has been tremendous growth in the total number of eCTD submissions sent to FDA. Table 1 provides monthly eCTD submission statistics from FDA.

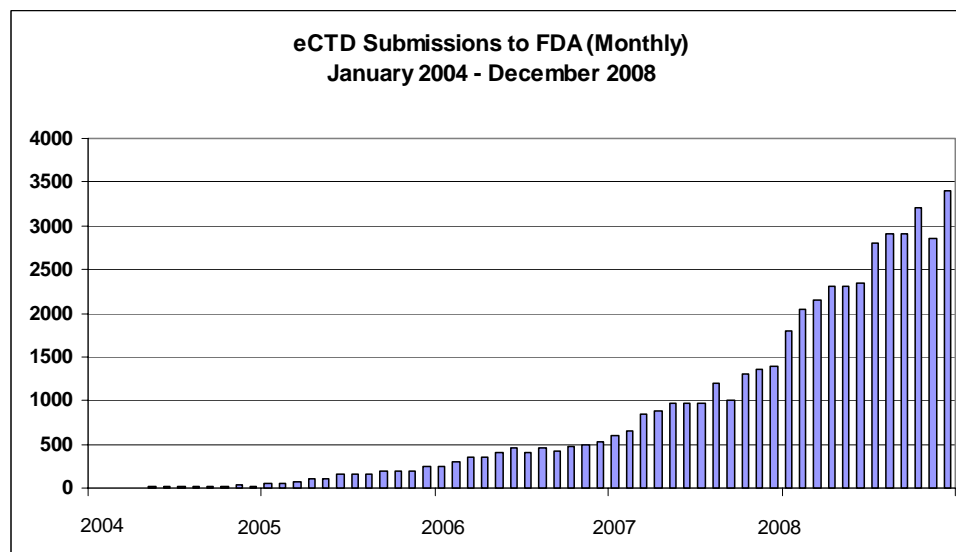


Table 1: eCTD Submission Statistics

These statistics are from the Office of Business Process Support of the Center for Drug Evaluation and Research at FDA¹. During the period 2005 to 2008, eCTD submission volume grew at a compounded annual growth rate of approximately 300%.

Beyond the total number of electronic submissions to FDA, it is also important to understand the growth of eCTD as a fraction of total submissions. In 2007, eCTDs represented 10% of total submissions to CDER. By February 2009, eCTDs were 20% of the total received². It is not unreasonable to expect that by the end of 2012, eCTD submissions may represent 40 or 50% of total submissions to CDER.

> eCTD the “Preferred” Format at FDA

The growth in popularity of eCTD is remarkable, considering that all of this growth has occurred without a “mandatory” requirement from FDA. Effective January 1, 2008, electronic submissions must be in eCTD format. Paper submissions are still acceptable and no date has yet been announced for an electronic-only requirement for original applications.

FDA representatives are increasingly speaking in favor of the eCTD. For example, at the Drug Industry Association (DIA) conferences on eCTD and Electronic Document Management in 2008 and 2009, eCTD was described as the “agency’s preferred format”^{3,4}. In pre-IND and pre-NDA meetings, it is not uncommon for review personnel to indicate their preference for eCTD or to request that submissions be made in the eCTD format.

> eCTD Leads to the Regulated Product Submission

The Regulated Product Submission (RPS) standard, developed by the Health Level Seven (HL7) organization, is a key element in the FDA bioinformatics vision for a “fully automated and interoperable infrastructure for managing the exchange of regulatory product information⁵.” A powerful structure, the RPS will provide for two-way electronic flows of information, providing an efficient conduit for review comments and questions to move from the regulatory agency to the sponsor. Designed with far more flexibility than the eCTD, RPS is intended to be used for applications related to drugs, devices, veterinary products and more.

Sponsors can use experience gained with eCTD submissions to prepare for FDA adoption of the RPS standard. As RPS is implemented, those who have adopted eCTD will likely be at a strong advantage, having already developed their electronic workflows and electronic submission preparation competencies.

3 – The Decision to Adopt eCTD

> Drivers for Sponsor Company Adoption of eCTD

For some sponsor organizations, the strong industry adoption trends, and the agency’s clear preference for eCTD are reason enough to adopt. Others believe the navigation, ease of review and data transparency that the format provides improves the quality of the submission and the efficiency and thoroughness of the review. Others may have made their decision following a direct request from agency personnel related to a specific application.

Use of the eCTD may also enable an organization to achieve important internal benefits, for example:

1. reducing the use and costs associated with producing and storing paper dossiers,
2. increasing the use and value from electronic document management system deployments,
3. streamlining the workflows in development, regulatory and marketing departments,
4. facilitating collaboration between teams of document authors, reviewers, publishers and external partners,
5. providing for efficient re-use of documents and submission components for projects involving applications to global regulatory agencies,
6. enabling a more effective ability to respond to agency questions,
7. supporting efficient and effective submission lifecycle management,
8. providing a convenient mechanism for information sharing during licensing, marketing and other business partnership transactions.

Taken together, these benefits may represent substantial cost savings and efficiency gains over the pre- and post-approval lifetime of a project.

> Potential Risks of not Using eCTD

Sponsor companies who are hesitant to adopt eCTD may wish to consider the potential risks of the traditional paper approach. As the eCTD format becomes even more widespread, there is increased likelihood of an eventual mandate from FDA. The recently implemented requirements for electronic submission of drug establishment registrations and drug listings provide a strong demonstration of the FDA's ability to impose electronic requirements.

Preference for the eCTD among FDA review personnel may ultimately leave paper submissions at a disadvantage. While current PDUFA review period targets are not different between paper and electronic submissions, it is possible that future targets will be set according to submission format. And it is also possible that the ease of review of eCTD will reflect in a reduction in actual review times for eCTD format submissions.

Sponsors planning or considering submissions to more than one jurisdiction, either directly or through marketing partners, may disadvantage their business strategy by pursuing paper submissions. It can take more time, effort and cost to produce additional paper submissions compared with the efficient re-purposing of content that the eCTD enables.

Sponsors planning to submit a paper IND or NDA may wish to consider the risk of having to make an unplanned and potentially last-minute conversion to the eCTD format. This change may be due to either an FDA mandate or the result of a request by FDA representatives that is communicated in a pre-IND or pre-NDA meeting. Such a conversion could divert critical focus from the submission content, and possibly delay the filing and subsequent approval.

4 – Common eCTD Adoption Barriers

> Costs to Establish and Maintain a Publishing System

The upfront and ongoing costs to establish and maintain an electronic publishing platform represent a significant barrier to eCTD adoption. The principal upfront cost components are as follows:

1. publishing software and hardware,
2. system and process validation,
3. training for system administrators and publishers.

Ongoing expense components are as follows:

1. publishing software maintenance and support fees,
2. system administration and operations,
3. publishing operations (staff).

In total, a system of very modest capacity might represent a total capital commitment of \$200-\$300K in the first year. The cost of the software alone is a small portion of this. With one or two dedicated resources for administration, maintenance and publishing operations, ongoing expenses might range from \$100-\$200K annually. Capital and first-year expense together represent a total potential requirement of \$300-\$500K. A software-as-a-service (SaaS) option for the publishing system might allow this total to be reduced by \$50-100K, yielding a total potential requirement in the range of \$200-\$250K for a system with limited capacity.

> Effort to Establish and Maintain a Publishing System

Effort to establish and maintain a system can be substantial. To put a system in place, a small team of resources is typically required to accomplish the following:

1. definition of requirements,
2. product research and evaluations,
3. system procurement,
4. system installation, configuration, testing,
5. validation documentation and execution,
6. FDA eCTD pilot execution,
7. FDA Electronic Submissions Gateway (ESG) pilot execution.

While every implementation project is different, a typical time-frame to complete all of the above steps might be 9-18 months, depending on the system size and configuration complexity.

> Risks of Failed Submissions

Every electronic publishing system implementation carries with it the risk of failed submissions. To produce compliant eCTD submissions requires a deep knowledge of the regulatory requirements and specifications for eCTD, as well as an ability to configure and operate a publishing platform to correctly assign every document-level and submission-level attribute. To develop deep subject matter expertise in both of these domains requires talented people and an organizational commitment to train and support these individuals so they may acquire and maintain this expertise.

5 - Overcome eCTD Adoption Barriers with Outsourcing

Given the initial costs (\$300 - 500K) described in the previous section, it is clear that the implementation of an in-house system is difficult to justify for a sponsor with modest submission requirements on an annual basis.

These sponsors and others may well find a solution in eCTD outsourcing, collaborating with a service provider or partner company experienced in eCTD publishing and equipped with a high-capacity platform.

Many original eCTD submissions (e.g. INDs, ANDAs, and smaller NDAs) may be published by a service provider for between \$10K and \$50K, less than 20% of the first-year costs of an in-house system.

For companies with a focus on early-stage development, with only IND applications and associated amendments to submit, the business case for an in-house platform is difficult if not highly improbable. Equally, a sponsor with one NDA or a small number of ANDAs to submit annually is likely to find the economics of outsourcing far more favorable.

Outsourcing may also save the time and effort involved in a sponsor's establishing and maintaining an in-house publishing system, leading to immediate eCTD capability versus a 9 - 18 month delay.

Outsourcing can also offer substantially-reduced risk of failed submissions. A professional service provider with an extensive eCTD track record likely has the expertise necessary to help a sponsor successfully navigate all of the complex regulatory and technical details of their electronic submission.

Finally, outsourcing may represent an attractive short-term option for sponsors to gain eCTD experience and develop their eCTD knowledge even if their long-term plan is to implement an in-house system. Equipped with real eCTD experience, a sponsor will be better-equipped to assess their requirements, select the best solution, and understand the effort associated with implementing, operating and maintaining a publishing system.

6 – Conclusion

The eCTD is the preferred format for regulatory submissions to FDA and offers considerable strategic benefits to sponsor organizations.

The most important question related to eCTD adoption is not “if” or “when” but “how”.

For many sponsors, outsourcing offers a compelling option to achieve the benefits of eCTD while significantly lowering the cost, effort and risk barriers.

References

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5 – Armando Oliva, *Bioinformatics Modernization and the Critical Path to Improved Benefit-Risk Assessment of Drugs*, *Drug Information Journal*, Vol. 42, pp. 273–279, 2008.