

Leveraging Technology to Increase Efficiency and Quality for Regulatory Submissions

Patricia Sichort, BS

Senior Regulatory Specialist,
Submissions Management,
Global Regulatory
Operations, Wyeth
Pharmaceuticals,
Collegeville, Pennsylvania

Teresa Booth-Genthe, MS

Senior Director, Submissions
Management, Global
Regulatory Operations,
Wyeth Pharmaceuticals,
Collegeville, Pennsylvania

Over the past 5 years, we have implemented several technologies (including eCTD, digital signatures, and the use of FDA's Electronic Submissions Gateway) in the regulatory submissions arena that have enhanced the quality of submissions and improved the efficiency of the submission generation process. In addition to technologies specific to a regulatory submissions group, tools and technologies have been

implemented reaching back into the organization to the groups that generate the individual submission components. This article outlines the programs and technologies implemented, which have increased productivity of the submissions staff by more than 30%, while reducing overall spending (full-time employee and capital) by over half a million dollars a year and increasing the overall quality of the dossiers.

Key Words

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Correspondence Address

Patricia Sichort, 500 Arcola
Road, Wyeth
Pharmaceuticals,
Collegeville, PA 19426
(email:
sichorp@wyeth.com).

THE ELECTRONIC AGE

From submission planning through archival, industry continually strives to implement technologies to aid and improve the flow of information within the company, to business partners, and ultimately to regulatory authorities. By embracing technology and having a willingness to change business practices upstream, we have shown that many efficiency and quality improvements can be realized in a short time frame and can position a company to actually do more with less. Table 1 is a high-level summary of some of the realized gains from programs and initiatives implemented at Wyeth that are discussed in this article.

DOSSIER TRACKING AND PROJECT MANAGEMENT

A major pharmaceutical company may have over 100 active compounds in development, and numerous compounds on the market that require the management and tracking of amendments and supplements to agencies around the globe. In addition to the numerous daily submissions, a major dossier may consist of thousands of documents and data files in different formats that require different processing paths. To help manage this workload, we implemented View-Point, a submissions management tool created by Octagon Research Solutions. This tool has enabled us to manage submission activities and

resources, monitor and manage submission-related issues, and report meaningful metrics. By using a work flow management tool, we can share workload across sites seamlessly and take full advantage of each FTE and full advantage of our global staff. We routinely pass on tasks to publishers in other regions via the system, taking full advantage staff in other time zones. For example, personnel in the United States can complete linking a summary of clinical safety that was started by personnel in the EU. This becomes particularly useful when publishing major supplements or original marketing applications when the individual component load is high.

By knowing the actual workload of each publisher and being able to quickly transfer tasks via the system, we have been able to reduce the reliance on contractors during those peak times and have been able to reduce overall staff by 5% during nonpeak publishing times.

In addition to sharing work, it is now possible to accurately monitor and ensure resolution of all submission issues prior to dispatch. This issue tracking has increased the quality of each submission and has facilitated identifying organizational problem areas. An example of how the system was used to identify and monitor a problem area concerned submission component readiness. In 2004, the overall rate of return for documents not being submission ready was well over 50%, and in some areas of the business the

TABLE 1

	Realized Gains			
	Based On	FTE Savings	Est. Monetary Savings	Quality Improvement
Conversion to eCTD	2,000 components/ 400 volume dossier	>200 hours	\$250,000/NDA Elimination of paper copies	Component life cycle; QC for consistency
Electronic Submission Gateway (ESG)	3,000 US submissions	>300 hours	\$450 media \$24,850 shipping \$150,000 equipment	Flexibility of dispatch time; elimination of tracking status
Validation tool	3,505 submissions 27,000 components	>810 hours	N/A	Additional QC step that removes human error; customizable to region and batch QCs valid links
Automated linking	2,600 links on a tabular listing of CRFs	>13 hours	N/A	Removal of human er- ror; ensures that every file is checked
Electronic archiving	Major dossier (300 boxes)	~12 hours	\$1,017/first year	Submissions can be re- trieved immediately; archived copies are less likely to become damaged
Work flow management tool	18 months of usage	5–10% reduction in head count and full utilization of staff	N/A	Transparency of issues; accurate and re- portable metrics; stan- dardization and har- monization of processes
Submission-ready components (SRC)	Return rate metrics for non-SRC	Reduced cycle times and rework	N/A	Harmonized compo- nent format; intradoc- ument hyperlinks; ad- herence to guidance

return rate was close to 100%. The publishing group was able to supply management real-time data of how many components had to be reissued and how much time was spent reprocessing those components due to improper document formatting, fonts, and so on. Due to the widespread issues and the documented delay in dossier building, the company instituted a submission-ready component (SRC) program. This program rectified the majority of the issues and has resulted in decreased effort and increased quality of submissions. This program is discussed in the next section.

Throughout this article, data from the work flow management tool are presented to illustrate

the overall decrease in time or increase in quality (by the reduction of identified issues) of the processes and technologies implemented.

AUTHORING COMPONENTS SUBMISSION READY

The concept of the SRC is a component that, when the publishing group receives it, is ready to be built into the submission (ie, content is complete and accurate, formatting is in accordance to standards set to regulatory authority and company requirements, and intradocument bookmarks and hyperlinks are correct). Before initiation of the SRC program, documents were received with varying page sizes, inconsistent

headers, improper fonts, and so on, and had to be returned to the authoring department for corrections, a cycle that could be repeated multiple times for a single document. The company initiated a program to standardize, streamline, and harmonize submission documents and to have authoring departments deliver documents truly submission ready. The initiative included a three-pronged approach: first, the development of a company-wide MS Word template; second, improvements to the PDF rendition server; and last, development of content shells.

MS WORD TEMPLATE

To increase efficiency and quality of publishing, all documents that can be submitted to a regulatory authority should be generated using a standard company template. The use of a template in the authoring program (eg, MS Word) allows for customized styles for document text, section headings, table and figure titles, and endnotes. Custom macros can be added to standardize margins, tables, cross-references, and more. Once a template is developed, company-wide training and local experts need to be organized to support usage. By having one company-endorsed template and required training, document formatting is standardized across all departments.

RENDITION SERVER

Normally after a document is authored, it is rendered to a PDF and then processed to include intradocument bookmarks and hyperlinks. The degree of post-PDF processing can be greatly decreased by interfacing templates with the rendition server. During the conversion process, the rendition server can interpret information coded within the MS Word document to automatically produce intradocument navigation. The section headings and table and figure titles all convert to bookmarks. The table of contents, list of tables, and list of figures are all automatically linked to their correct locations. Intradocument hyperlinks are automatically added to cross-references and endnote citations, but links to content on the same page are removed, further reducing the need for

post-PDF processing, and thereby eliminating human error.

CONTENT SHELLS

Content shells take the concept of component standardization and efficiency a step beyond templates. Content shells can be developed for all components routinely found within the CTD structure, from summaries to clinical study reports and across business units: small molecules, biopharmaceuticals, and vaccines. Each shell is based on the company template and populated to include appropriate standardized content and instructional text to guide the user when authoring the components. Content shells reduce time spent authoring and formatting, decrease variability between submissions, and homogenize the appearance and language of a company's submission documents. To make the shells accessible, yet protected against unauthorized alterations, they should be maintained in a document management system. Document management systems offer a single location where components can be written, reviewed, revised, approved, and archived.

The impact of the MS Word template and the enhanced rendition server is depicted in Figure 1, which illustrates the rate of return of non-compliant documents from the publishing group. The return rate dropped from greater than 25% in third quarter 2006 to less than 5% in second quarter 2007. The introduction of content shells, implemented in late 2007, is just beginning to be realized and data are not yet available to be presented here.

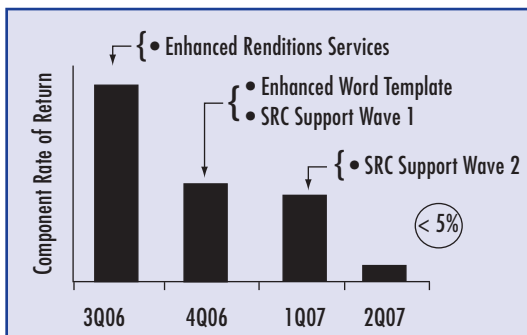


FIGURE 1

Component rate of return.

eCTD SUBMISSIONS

Adoption of the Common Technical Document (CTD) in the major markets may be the single most influential factor in increasing efficiency and quality of submissions worldwide. The benefits of moving from CTD to the electronic CTD (eCTD) format for health authorities have been detailed in publications and presentations over the past few years. This article focuses on the impact of eCTD adoption from a sponsor perspective.

As the eCTD is electronic and its structure standardized, it is possible to reuse portions by “cloning” relevant sections for submission to other regions, provided that the documents were written for global usage. It is important to determine the submission strategy early, so that documents can be written for the correct target audience. Reusing submission components by cloning eCTD sections eliminates the need to rewrite documents and preserves the publishing work (navigation across documents), making simultaneous submissions to eCTD regions possible. For regions that accept non-eCTD electronic submission (NeES) format, but are not eCTD-ready, the time to produce second-wave country submissions from existing eCTD submissions may only be weeks or even days.

In addition to the efficiencies, there is also an increase in the quality of submissions by:

1. Quality control of references: Hyperlinks in eCTD submissions are required and increase the quality of a submission by adding an inherent review. As interdocument hyperlinks are added, the references within each document are checked (eg, is this report truly in module 4 or does it belong in 5.3.1.4? This clinical study report references three investigators, but only two curriculum vitae were included; which is correct?).
2. Reduction in human errors: Electronic cloning of the core dossier across regions reduces the human error of rebuilding and relinking the dossier.
3. Identification of missing documents: As the eCTD is usually built in an outline fashion, it is easier to identify missing or inadvertently omitted documents. Templates can be developed based on company requirements for submissions (ie, placeholder for the ISS and ISE in Module 5).

By adopting the eCTD as the single platform for applications, a company can achieve the efficiency and quality enhancements noted above and will also be able to focus the publishing staff’s skill set. The single-platform approach will enable the publishing group to harmonize processes globally, allowing publishers to share work across sites. In-house this has ultimately resulted in a reduced number of staff processing more submissions globally.

ELECTRONIC SUBMISSIONS GATEWAY

The FDA implemented the Electronic Submissions Gateway (ESG) in 2006, and since its inception has processed over 180,000 submissions (1). Sponsors can either submit via an AS2 gateway using commercial software or via the FDA web portal. By either method, the ability to send submissions electronically results in both hard savings (paper, media, shipping, printers, etc) and soft savings (the number of FTE hours spent over the course of a year printing, sorting, tabbing, binding, burning electronic media, and packaging submissions) for the sponsor.

Currently submissions under 10G can be dispatched to the FDA via the ESG. We have documented that savings from using the ESG include 20–25 hours in FTE effort per month and a significant monetary savings for printing major dossiers. For regions still requiring paper, our publishing group shifted printing responsibilities to a centralized contract organization, reducing number and cost of printers, thereby obtaining departmental hard savings on equipment of over \$150,000 per year.

PUBLISHING TOOLS

After a submission has been compiled and processed, we validate eCTD submissions using several validation tools. Many validators check not only for eCTD xml requirements, but also for valid hyperlinks, including broken or absolute links, thus resulting in significant time savings over performing these checks manually. As an example, when a submission containing 2,620 PDF files was validated as a whole, and not one file at a time, a savings of more than 80 hours

was realized. In 2007, the publishing group processed over 27,000 components. Using the validator to check for links saved the company the equivalent of over 810 FTE hours.

It is not always necessary to look outside the company for labor-saving tools. It is often the people who are mired hip-deep in everyday tasks who discover creative time-saving solutions. For instance, using a macro or PDF plug-in tools to automate key word or list linking can increase quality and reduce time to publish. Based on actual data, we calculated a 30-fold decrease in the time it took to link a list of CRFs for an original dossier (approximately 2,600 links created) and the quality improved due to the reduction of human error.

ELECTRONIC ARCHIVING

The archival process, generally the final step in the submission process, requires filing a complete and identical copy of the submission in a controlled location. Traditionally, this has meant that a full paper copy, complete with color-coded binders and tabs, had to be prepared simply to be stored in the records room for years before being sent to a warehouse for permanent storage. Depending on the number of submissions created over the course of a year, usually an enormous amount of space is needed to house those volumes. For example, in 2006 we submitted two original New Drug Applications. Combined, those submissions totaled 350,760 pages (not including the non-PDF pages). Had they been paper submissions, over 1,100 volumes would have been archived. Those volumes would have had to find room beside all of the other submissions produced in a typical year, including thousands of safety, protocol, and investigator submissions, and hundreds of other amendments and supplements. It is hard to imagine that much real estate being used simply to store submissions, not to mention the staff required to oversee, index, file, maintain, and photocopy them when the need arises. As the majority of US submissions are in eCTD format and dispatched through the ESG, these submissions can be archived directly into a document management system. As a result, they can be imme-

diately accessed by in-house personnel and the costs to maintain them are greatly reduced. These savings and efficiencies can only be realized if a company has already implemented an electronic-only submission platform and usage of the ESG. Though not as great, sponsors can still save by moving to an electronic format even if ESG is not utilized. Physically archiving electronic media, such as CDs, DVDs, and digital linear tapes, will require significantly less space and effort than the same submissions in paper format.

FINAL THOUGHTS

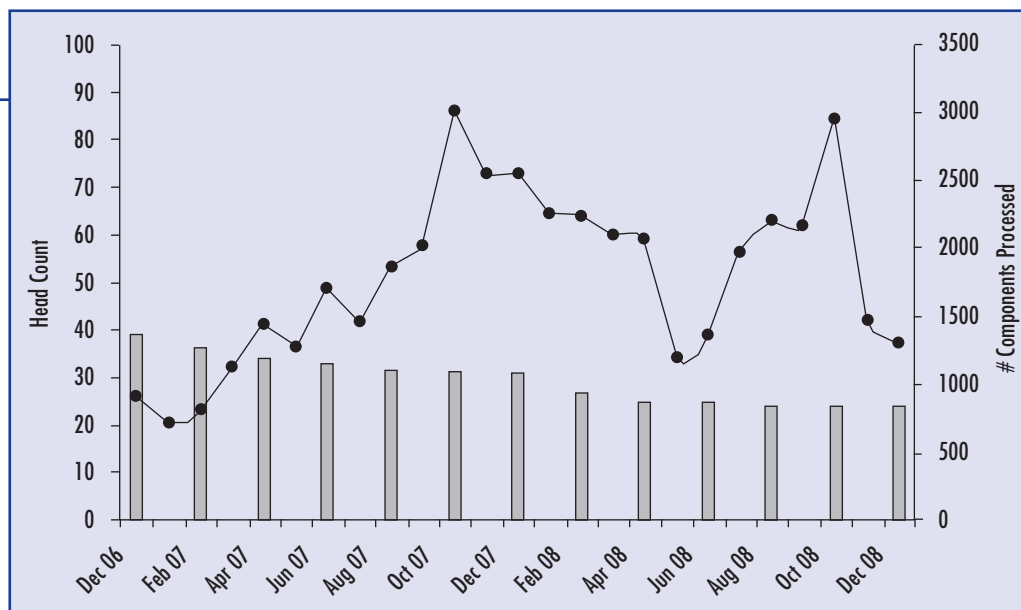
Adopting an electronic platform brings forth manifest and proven efficiency and quality improvements. By implementing the tools and processes mentioned above, Wyeth's submission publishing group was able to absorb a >20% decrease in FTEs while increasing the number of individual components processed (see Figure 2). The company was able to improve the quality of submission components received by completing the implementation of an SRC program combined with the metrics and accountability gained by using a project management tool.

In the industry today, regulatory authorities are moving toward electronic-only submissions. As of January 2008, the Center for Drug Evaluation and Research (CDER) requires submissions be made in the eCTD format and the Center for Biologics Evaluation and Research (CBER) strongly recommends it. The European Medicines Agency (EMA) accepts electronic-only submissions in the context of centralized procedures as of January 2009, and many national agencies are requiring electronic submissions in CTD format and or eCTD. Health Canada has initiated steps to fully adopt the eCTD for drug submissions with the initiation of a "hybrid program" that allows for full eCTD and reduced co-submission of paper (2) and SwissMedic and the Therapeutic Goods Administration in Australia have announced their plans to accept eCTD submissions within the next year.

Looking for ways to streamline processes and workflows and maximize efficiency and quality will always be an ongoing effort. As regulatory

FIGURE 2

Head count versus documents processed by the submissions staff.



authorities and sponsors continue to move toward fully electronic submissions, new technologies, processes, tools, and techniques will continue to appear. If, as an industry, we are open-minded and welcoming of new ideas and implement them in a timely manner, we will continue to grow and improve.

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