Switching to Electric

As the future becomes increasingly digital, regulatory authorities are beginning to harmonise and adopt standards to introduce electronic and virtual documents. If organisations act now, they will not only achieve compliance, but will improve their efficiency and reduce costs associated with the submissions process

Darryl Clarke at Sciformix Corporation

More than ever before, life sciences organisations are being challenged to bring new and improved products to market faster, with fewer resources and in an environment where failure to comply with regulatory requirements can result in costly penalties. In addition, companies are expanding into new geographical areas as they pursue business expansion, mergers and acquisitions, and extension of product longevity. This need to cater to disparate requirements across regions can, in many cases, slow down processes and reduce operational efficiency and profitability, while delaying time-to-market of these products.

Furthermore, regulatory mandates are becoming more stringent and the need for automation, technology, process excellence and global knowledge is paramount. Great strides have been made within the industry to harmonise these requirements and the adoption of standards like Common Technical Document (CTD), electronic Common Technical Document (eCTD) and non-eCTD electronic Submissions have simplified and streamlined interactions with health authorities. In addition, to comply with the evolving regulatory mandates, cope with higher volumes and manage the resources that are spread across multiple geographies, firms are turning to outsourcing, and are partnering with vendors that specialise in regulatory affairs and operations.

New Systems

Successful, compliance-driven companies are optimising processes, adopting standards and deploying technology solutions with the global market in mind. Electronic submissions are becoming a way of life, not only from a regulatory standpoint, but also from an efficiency point of view. While eCTD software has transformed many of the previously manual processes, technology alone is not enough. New systems and processes that require a new skillset have emerged.

Since 2003, the FDA has provided applicants with the option of submitting CTDs in an electronic format. The electronic format – or eCTD – not only provides an interface for industry-to-agency transfer of regulatory information, but facilitates the creation, review, lifecycle management and archiving of the electronic submission (1). Last year, the FDA mandated that all regulatory submissions be made electronically to facilitate a more effective review process and information sharing (2). When the final guidance for all submission document types detailed in Section 745A(a) of the Federal Food, Drug and Cosmetic Act is provided early next year, the FDA has stated that industry will have until the first quarter of 2017 to implement a full transition to eCTD submissions for all document types listed in Section 745A(a) (3,4).

Compliance can be facilitated through an outsourcing model, which aims to achieve operational excellence via optimised processes, understanding of various global standards and well-trained experts – ultimately resulting in timely approvals.

Figure 1: Paper submission process

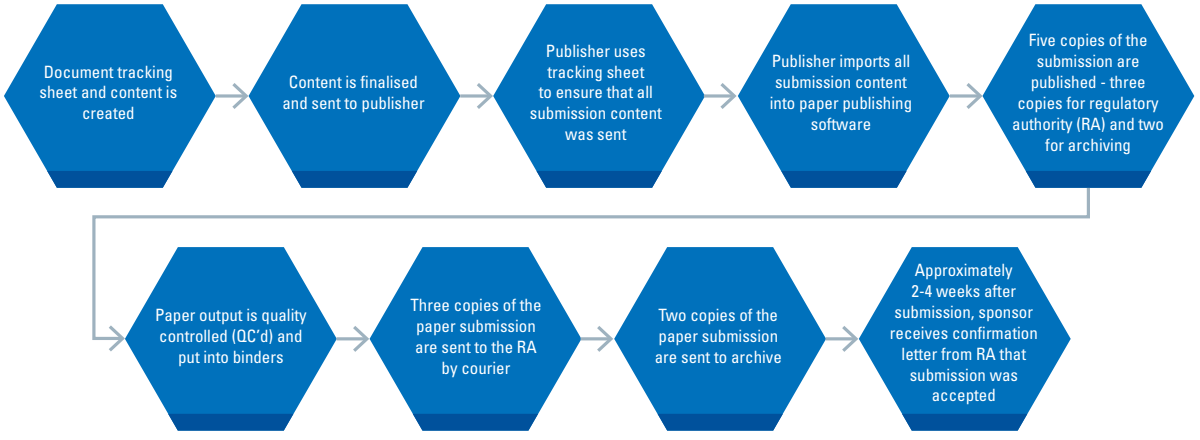

Figure 2: Electronic submission process

Technical Expertise

As companies move to electronic submissions, those who are involved in eSubmission work will require a different skillset to those working with paper files.

The documents specialist will need to have advanced technical expertise and experience with: virtual document (vDocs) creation/submission/archiving – for example, templates to create clinical study reports; document management systems, such as FirstDoc, ddms; publishing software like Insight Publisher, eCTDXpress, DocuBridge; and other systems – for instance, ISI Toolbox, Adobe Acrobat features such as PDF bookmarks and hyperlinks, OCR and file optimisation, ISI Writer and MS Word, including macros. In addition, they will need to have in-depth knowledge of eCTD ICH guidelines and the content of common regulatory documents in order to independently assess the quality and completeness of typical components – for example, main body, appendices, attachments and source documents.

The eSubmission publisher will need to be skilled in creating electronically published proposals, reports, and regulatory documents and dossiers using a variety of software. They will need to perform critical quality assurance compliance checking, formatting, hyperlinking, bookmarking and review of documents that results in the rendering of multiple documents to PDF. They will also need to have experience and knowledge of reproducing Modules 1-5 in eCTD format, in order to provide component-level publishing and submission support to guarantee conformance to eSubmission standards.

Finally, the eSubmission manager will need to maintain effective interactions with all publishing and submission contributors to ensure timely delivery of submission-ready documents.

In addition to obtaining new skillsets, companies will need to implement new processes. Again, this can be outsourced to specialised vendors that have best practice models already in place. The old paper submission process is depicted in Figure 1, and the new eSubmission process is outlined in Figure 2.

Benefits and Challenges

The standardisation that eSubmissions have brought will allow for much greater consistency for the FDA and other organisations. All parties will benefit from reducing automation and storage costs by having all data in a common electronic environment. This will also allow for easier management of documentation and oversight of products more efficiently, eliminating difficulties with accessing, searching through and finding data in paper format.

A common global standard for electronic submission of quality, safety and efficacy information provides many benefits, including:

- Enhanced ability to efficiently organise, prepare and manage submission content
- Reduced storage costs associated with producing and storing paper dossiers
- Streamlined workflows in development, regulatory and marketing departments, while increasing collaboration between teams
- Streamlined review process, allowing for multiple reviewers and a more efficient review process
- The reuse of documents and submission components (5)

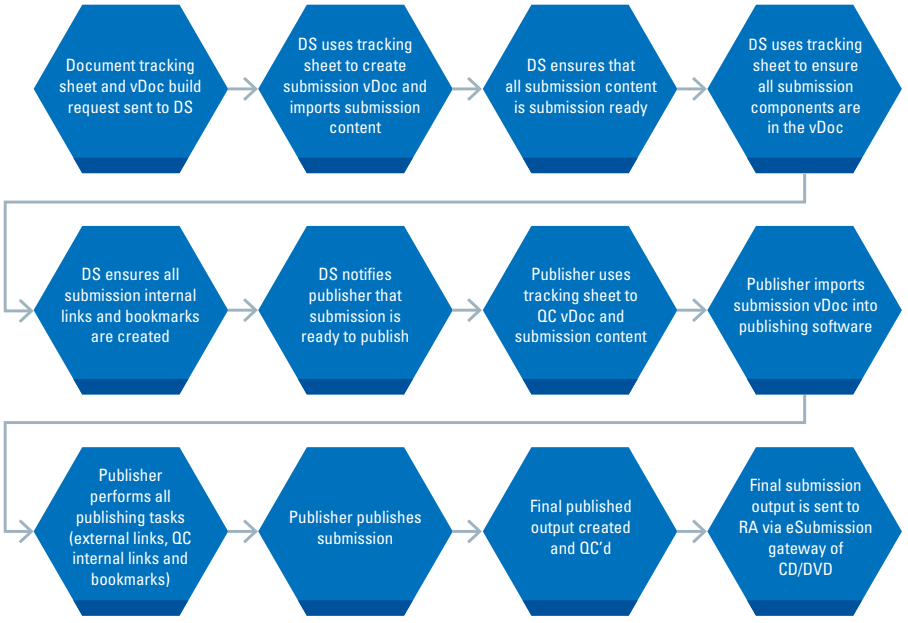

Figure 3: Small projects process

Despite these advantages, the mandatory switch to eCTD presents companies with several challenges. The costs, both in initial capital and annual expense of building, validating and operating an electronic publishing system, together with the training and administration needed to develop organisational competency, present significant barriers to adoption. The effort required to establish and maintain an in-house system can be substantial, and a team of resources is typically required to: document the requirements; research and evaluate options; procure, install, configure and test the system; and validate documentation and execute the full solution. While each organisation's implementation project plan is different, a typical timeframe to complete the required steps is estimated to be between 9-18 months, depending on the system size and configuration complexity.

Another barrier to adoption is the risk of failed submissions. A deep knowledge of global regulatory requirements and the specifications of eCTD, as well as the ability to configure and operate a publishing platform to correctly assign every submission-level and document-level attribute, is required in order to produce compliant submission documents.

While large pharmaceutical companies have the required capital and regulatory expertise for full eCTD implementation, firms operating across their global business models in emerging markets may not – particularly when considering the dynamic nature of regulatory requirements across both emerging and developed markets. The same can be said of small to mid-sized pharmaceutical businesses operating in developed markets. For these companies with modest submission requirements on an annual basis, it is clear that the implementation of an in-house system is difficult to justify.

Proactive Approach

As a result of the growing submissions needs and ever-changing regulatory requirements, successful organisations are developing new strategies and a proactive approach to eSubmissions. They are increasingly looking to specialised outsourcing vendors to oversee, manage and perform regulatory operations tasks. This can provide cost-effective and flexible means to manage the varying degree of regulatory demands, such as expertise/knowledge, resource flexibility, additional capacity, process improvement and process standardisation. Companies need to take a more holistic approach to regulatory submissions through engaging earlier in the process, and by setting-up submission infrastructure capabilities with project/product managers to align processes and timelines.

The future is electronic, seamless, interconnected and automated. A global regulatory best practice model not only reduces costs and increases efficiencies, but also enhances an organisation's ability to respond to changes in the FDA final guidance. A best practice model can be customised for each project and is dependent on the firm's requirements and size of the project through enhanced productivity and quality, use of innovative processes, people expertise and technology.

Small Projects

For small projects – such as clinical study reports, advertising/promotional materials submissions and small supplements/amendments (those under 1,000 pages) – a document specialist (DS) should be put in place to work directly with a team of content creators and authors. This will ensure that all pieces of the submission are created and finalised according to the required timelines and guidelines. The process should commence with the content creators and authors who are responsible for the authoring, reviewing and approving of all submission content. Initial content should then be handed to the DS to oversee and facilitate all document control procedures, including:

- Formatting of all documents
- Ensuring documents are 'submission ready'
- Creating submission vDocs that all submission components are linked to
- Creating a submission tracking tool to ensure all components of the submission are processed and accounted for
- Quality checking the submission output

An optimised best practice electronic submission process flow for small projects is set out in Figure 3 (see page 58).

Medium to Large Projects

For medium to large projects – including investigational new drug applications, new drug applications, biologics licensing applications and new drug submissions – a submission management team (SMT) and publisher should be added to this structure to liaise with the DS and the content creation team to ensure that all projects are completed and published successfully. Within the model, the SMT should work with the DS to guarantee that submissions are ready within the required timelines.

In the final step of the process, the publisher will receive the final submission after a high-level quality review process, utilise the submission tracking tool to guarantee that all components are accounted for and publish the submission. The publisher will then work with the DS and content creation team to quality control the final published output. Once everything is checked and confirmed, it can be transferred to the regulatory authority.

An optimised best practice electronic submission process flow for medium to large projects is depicted in Figure 4.

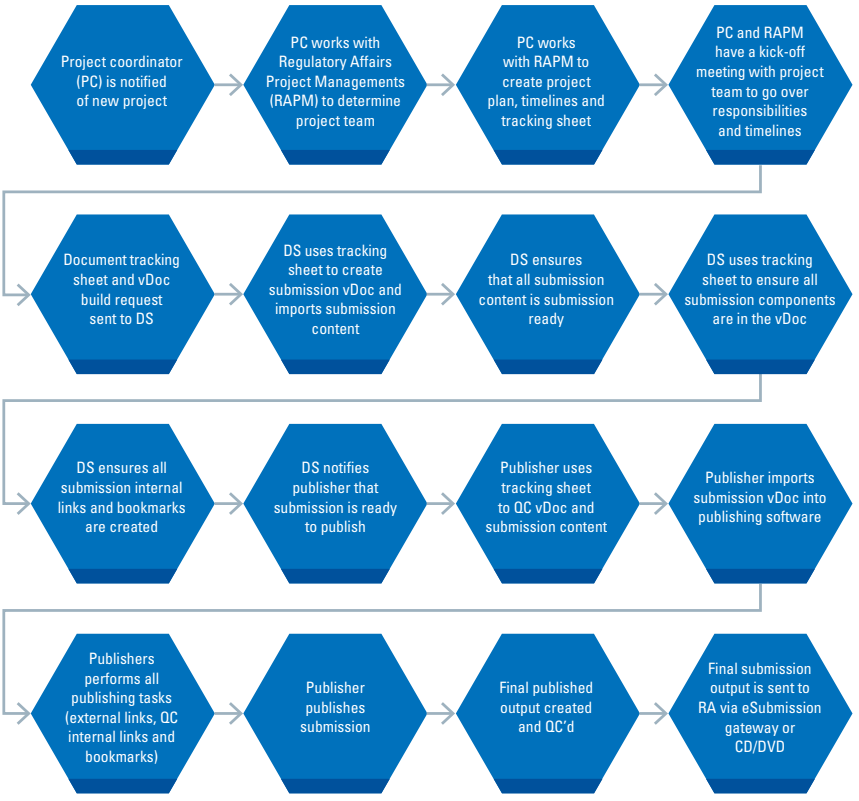

Figure 4: Medium to large projects process

Forward Thinking

While great strides have been made within the industry to harmonise requirements to comply with evolving regulatory mandates, cope with higher volumes and manage resources spread across multiple geographies, organisations should feel a sense of urgency and take the opportunity to change their model and how they work.

The future is becoming increasingly digital and submitting documents electronically benefits all parties. However, the costs and regulatory operations expertise associated with the process changes involved and new technologies required to remain compliant are of chief concern for pharmaceutical companies. Looking forward, firms should be preparing for eSubmissions – and not waiting until final guidance is released. It should be a priority for all to have the appropriate systems in place, or to be working with a service company that meets their needs, in order to adopt a proactive approach to eSubmissions. This best practice model will ensure that organisations successfully achieve compliance with regulatory requirements, while also increasing efficiency and reducing costs of the submission process.

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About the author

Darryl Clarke is Head of Global Regulatory Operations at Sciformix Corporation, where he advises pharma companies on building their regulatory operations strategies and eSubmissions departments. Previously, he worked for Baxter Healthcare, and was instrumental in helping to create its Global Submission Project Management group and was a key member of the team that helped convert the company products from paper to eCTD. Darryl has a BS in Computer Information Systems from the DeVry Institute of Technology, US.
Email: darryl.clarke@sciformix.com