Accelerating Global Submissions with a Six-Point eCTD Strategy

By Steven Dowdley and Chet Shemanski

This article discusses how an integrated, six-point electronic Common Technical Document (eCTD) publishing strategy can accelerate global submissions and enhance the efficiency of regulatory operations. In addition, it outlines challenges specific to: large companies with a well-established, eCTD-compliant publishing capacity, but may lack strategic agility; and smaller companies with limited eCTD resources and expertise.

The World - and Sponsor Challenges - are Getting Bigger

To maximize Return on Investment (ROI) for new drugs, sponsors need rapid approval in as many jurisdictions as possible. Today, emerging markets such as those of Brazil, Russia, India, China, Mexico and Turkey (BRICMT) economies are the source of an ever-larger portion of product revenues. These emerging markets are expected to represent a third of the global pharmaceutical market by 2016.¹ Their Compound Annual Growth Rate (CAGR) is increasing faster than those of mature markets such as the US and EU.

At the same time, shifting of product portfolios toward unmet therapeutic needs has increased the need to capture smaller patient populations across broader geographies. Delivering products to the right markets worldwide is as important to companies whose plan is to license or sell a product candidate as it is to those whose plan is to develop/maximize its value as part of their own portfolio.

Reusing Submission Content with eCTD Publishing

An effective Rest of World (ROW) submission process demands a flexible and efficient global regulatory operation. For example, the speed with which ROW submissions are obtained (as well as the absolute number obtained) has become a critical success factor for orphan (or ultra-orphan) drugs due to the hyper-competitiveness of the marketplace.
By executing a parallel global submissions strategy, one mid-sized company recently beat its own regulatory filing deadlines (and thus exceeded revenue expectations) for its drug to treat a genetic disorder affecting fewer than 2,000 people worldwide. At the end of an 18-month global submissions effort, this product was approved and placed on the market in more than 30 countries. The majority of the product’s sales growth comes from outside the US.

An electronic Common Technical Document (eCTD) publishing capability helped the company reuse appropriate submission content across countries and regions, thereby shortening timelines and conserving resources. This approach also allowed the company to reorder its sequence of submissions dynamically in response to changes in target markets during this 18-month period.

**Six Imperatives for an Effective Global eCTD Strategy**

Unfortunately, many companies are having difficulty improving the efficiency and flexibility of their global submissions. Large companies have complex infrastructures and well-established processes that can hamper agility, whereas small companies often lack global resources and expertise. A sound, compliant eCTD publishing operation can help both types.

A successful eCTD strategy:
1. harmonizes data, document and submission standards
2. optimizes processes to stay on top of evolving regulations
3. empowers authors with eCTD compliance tools
4. validates output for efficient publishing
5. uses an integrated, centralized, end-to-end regulatory information management (RIM) platform
6. scales regulatory resources nimbly for the task at hand

**Harmonize Data, Document and Submission Standards**

Harmonized standards are critical to a developer’s ability to collaborate globally with regulatory agencies (both region- and country-specific), with potential corporate partners and between internal project teams. Submission preparation, management and information sharing are more efficient when all parties use the same language (i.e., harmonized standards). Information prepared and submitted to regulatory authorities in support of product development and commercialization must be consistent, from one submission to another, and compliant, with both global and local requirements. By using harmonized standards, companies dramatically improve their ability to reuse core portions of their regulatory submission content from one country or region to another.

The benefits of adopting harmonized standards include:
- consistent look and feel of documentation/publications (regardless of production site)
- less rework of document content shared across sites and submissions
- compliance with regulatory submission requirements across all sites
- simplified training for new employees
- data sharing across marketing applications
- accurate reporting

**Optimize Processes to Stay on top of Evolving Regulations**

As pharmaceutical companies focus on global operations and speeding adoption of their products in all markets, many are scrutinizing the effectiveness of their RIM business processes. Many firms either do not document their publishing processes at all or rarely review them for necessary updates as the organization matures or new mandates and deadlines alter the regulatory landscape. This neglect can render Standard Operating Procedures (SOPs) outdated, inconsistent, irrelevant or even worse, non-compliant.

Optimized and well-documented business processes are critical for a global regulatory team to operate effectively and efficiently in today’s fast-evolving environment. Harmonized, consistent processes across corporate and subsidiary operating sites
optimize resource usage and efficiency, reduce cycle time and raise the quality of output with better compliance.

**Empower Authors with Tools That Create eCTD-Compliant Content**

Document structure and navigation are key aspects of a successful submissions review by regulatory agencies and support effective agency interactions (e.g., addressing agency questions) on the path toward regulatory approval. Often documents intended for regulatory submission are fraught with problems: incorrect formatting, lack of guidance-compliant navigation tools or improper file formats, sizes and structures. Any of these problems will cause the submission to fail validation, resulting in costly rework and delays in the regulatory approval process.

A robust, eCTD-compliant system allows authors to produce compliant documents from the start. Such a system should contain the following features:

- Templates, including content templates, with structure, guidance and regional CTD requirements (such as administrative forms) for the US, EU, Canada, Japan, etc.
- Embedded style formatting that persists should the file be opened in any other applications or outside of the author’s computer network or if the toolbar is not displayed.
- Macros, building on Microsoft Word, to bring commands under one tab, format tables and figures automatically so that everything is consistent, provide common symbols for medical technology and produce coded fields.

**Validate Output for Efficient Publishing**

The increasing complexity of global regulation makes it difficult to generate compliant regulatory submissions from both a content and technical perspective. Building validated output that enhances a regulatory agency’s ability to navigate and review a submission is vital to streamline the approval process and get a product to market in a timely fashion.

If a submission cannot be validated or accepted, the regulatory clock will not start ticking. Minor validation issues (often related to improper formatting) occur routinely and typically can be resolved easily; however, major ones can cause serious delays. Therefore, successfully executing a global submissions plan requires a team of qualified individuals supported by sophisticated software allowing them to efficiently formulate eCTD-compliant responses, regardless of time zone.

It also is important to consider ongoing maintenance of the original submission as it progresses through its lifecycle. Choosing the proper level of granularity, the location of documents within the submission and the format of documents can all impact a company’s ability to maintain the submission dossier over time.

**Use an Integrated, Centralized, end-to-end RIM Platform**

RIM is defined as the effective and efficient collection, storage, retrieval and communication of regulatory information. RIM processes include defining product authorization targets, managing regulatory submission plans, creating and gathering submission information, producing and submitting the submission output and managing product registration.

In many cases, the information required to support these processes is not managed centrally, making it difficult or impossible to quickly and accurately find definitive answers to questions such as, “What is registered where?” or “How many new registrations are planned this year?” An integrated, centralized, end-to-end RIM platform powerful enough to support the regulatory information workflow from the earliest stages of research and development, through a sequence of global submissions, to marketing authorization and product maturation is key to achieving regulatory operational excellence.

An integrated RIM platform drives harmonization, promotes standardization, improves collaboration, ensures compliance, eliminates waste, reduces costs, accelerates product release and allows companies to operate and to compete more effectively in global markets.
Scale Regulatory Resources Nimbly for the Task at Hand

For decades, the pharmaceutical industry has been outsourcing high-volume, high-frequency activities such as document preparation, dossier assembly and submission publishing. In the early days, pharmaceutical companies looked to staff augmentation and functional outsourcing to manage the peaks and valleys in their regulatory workloads. Now, as the industry shifts the focus of their regulatory staff away from those tactical and routine activities, a more robust outsourcing model is developing. The role of the service provider is becoming far more strategic and integral to the client’s core business.

Vendors of regulatory services must possess a thorough understanding of their clients’ strategies and the intricacies of the global regulatory landscape. They must effectively leverage a broad portfolio of resources, including deep industry expertise, a scalable global workforce and innovative technology solutions to help their clients execute on those strategies.

What’s Next?

For Large Companies

Large companies often have a regulatory infrastructure to routinely cope with global submissions, but perhaps not as quickly or flexibly as they would like due to their set global headcount and established processes. In a rigid model, overhead and infrastructure tend to dictate the submission plan. For these companies, it often makes sense to upgrade the current regulatory operations organization and process by:

- updating workflow by developing or purchasing new tools (Sops and/or templates)
- training authors to write compliant documents to be easily incorporated into the eCTD
- establishing an account for electronic submission gateway submission through the FDA portal

For Smaller Companies

Smaller companies, particularly those without extensive resources, may prefer to work with a partner to help design the workflow, establish the document delivery requirements, deliver eCTD components to the partner for compilation into the submission and to review the final submission for quality. For global submissions, smaller companies can benefit from a partner’s expertise on the ground. For example, the European Union has one shared health authority, but can have 28 interpretations of the governing directives, and subtle cultural nuances can present potential landmines.

The World can be Your Oyster, if...

Optimizing global submissions requires a modern, compliant information management and publishing infrastructure. As harmonization of standards among jurisdictions proceeds, a sound eCTD process can streamline and thereby accelerate the process of submitting to multiple agencies while mitigating the risk of delays and lost revenue.

Transitioning procedures, personnel and infrastructure to eCTD publishing can mean a significant investment in time and resources. Yet the worldwide trend toward making the eCTD format mandatory continues to gather momentum. Therefore, it is never too soon to begin.

References


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