WHITE PAPER

Raising the Bar for Regulatory Submission Document Quality:

A Collaborative, Transitional Approach

LITERA

Regulatory Affairs Operations teams rely heavily upon the Medical Writing Community for the delivery of comprehensive, quality content to be used in various marketing applications. The Medical Writers may be in-house or external, or the documents may have been acquired through a partnership, merger, or acquisition.

Regardless of the quality of the content, there exists a great risk to the success of the overall submissions process when the Microsoft Word documents themselves are improperly formatted or the documents contain unknown formatting issues.

This article explores the needs of authors, identifying the challenges of the formatting process, and defining the business drivers necessary to support an optimal environment alleviating this potential risk in the submission cycle.

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Submission Scramble

As the deadlines loom unwavering for a Regulatory Affairs Operations team (Reg Ops) to assemble the final components of a global electronic regulatory application, the race is between quality and time. The team is dependent upon multiple departments and medical writers to deliver the final versions of approved study reports, summaries, product information, and regulatory documents in a timely manner.

During the planning process, the timelines for authors are identified and reports are expected well in advance of the submission date. However, when departmental daily tasks pile up and constrained resources are spread across multiple projects, the timelines inevitably slip. From the writer's perspective, there is still time left to get the report into the hands of regulatory operations; therefore, the concern is not as great. Yet, from the perspective of Reg Ops and the Submissions Teams, the time buffers are not as forgiving, because the submission date remains fixed—even though the report deadlines have shifted forward.

The reality of the situation is magnified when Reg Ops realizes that the electronic versions of the reports have major formatting issues. Now, with little time to spare, they are faced with costly overtime hours to manually troubleshoot, find and then fix the formatting issues to meet the submission deadline.

Contributing Factors

Upstream in this process we identify several contributing groups of authors. The scope ranges from in-house authors, to external authors such as contractor writers or Clinical Research Organizations (CROs), to unknown authors, such as authors of documents that were obtained as a result of a partnership, merger, or acquisition.

For the in-house category, the departments represented may include Clinical, Pre-Clinical, Pharmacology, Toxicology, Chemistry, Manufacturing and Controls, Quality Assurance, and Regulatory Strategy. The technical and medical writers from each of these disciplines are experts in their respective fields, and clearly are adept in the writing process.

They focus their effort on the verbal quality of the data and final reports. Looking beyond the data, we expect the authors to be proficient in the general use of Microsoft Word for report writing.

Most likely, they have also heard of the importance of properly formatting their documents in order to achieve a standard corporate-wide look and feel for the documents. A minority of the authors may be aware of a few technical aspects of the formatting process that cause problems with the publishing software.

However, the problem arises not from the breadth of knowledge regarding formatting requirements, but in the details of strict conformity to the formatting standards. In situations where documents are created without adhering to formatting standards, a host of issues may originate that affect the downstream processes of submission compilation and agency review. During submission compilation, one key area that is impacted by inconsistent application of formatting standards is the rendering process.

The rendering process occurs at the point when Reg Ops sends the source file through a rendering engine. The engine converts the source Word document into a PDF file, and can apply additional formatting to the resulting PDF file. If the original Word document contained formatting errors in margins, headers, footers, symbols, pagination, language, and fonts, the document fails to render. Then, the Reg Ops team must expend their time and resources to troubleshoot, find, and fix the errors. For one document, this process can take from an hour to several days to complete. This last minute bottleneck impedes submission timelines and risks a delay in the final application.

The second key area impacted by inconsistent use of formatting standards is the agency review process. For an efficient review, it is important that the entire application flows seamlessly from one section to another. As a reviewer jumps between the table of contents and the technical sections and follows links between tables, figures, and hyperlinks, the reviewer wants to experience a consistent look and feel between the files.

Consistent formatting not only elevates the level of corporate identity, but it also simplifies the review process. Standardized formatting is a key component of readability; consequently, poor readability forces

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the reviewer to constantly perform visual adjustments during the review process. This, in turn, impacts the timeliness of the review process by causing the reviewer to stop midstream and slow down the review simply to adjust to different fonts, margins, abbreviations, links, and formatting.

How is an author to conform to these formatting requirements consistently—whether they are at the departmental level, the submission level, or the corporate level—or a combination of each? Why is it so important to Reg Ops that the authors follow the established guidelines? What is the real impact on the quality of the submission if formatting rules are not applied?

Formatting Foundation

To answer these compelling questions, an investigation into the availability and use of style guides is necessary. First, if a style guide isn't in place, there must be a mandate for the development of one. Some corporations have taken the initiative to develop in-house style guides, while others have a basic idea and modify formatting sporadically.

The development of an in-house style guide is a necessary joint effort between regulatory affairs and the authoring communities. A well-designed style guide merges regulatory review requirements with formatting technicalities to form the baseline for a corporate-wide look and feel.

Second, all contributing departments must be made aware of the existence of the style guide. A style guide can only be used by those who know it's available. Typically, Reg Ops champions the style guide, given the direct interest they have in the resulting clean set of documents.

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Third, the style guide must undergo an implementation phase. As succinct and beneficial as a guide may be, the real challenge exists when the authors begin adapting their writing process to incorporate the guidelines. Often times, best intentions for consistent formatting take a backseat to workload pressures. At this point, the authors can easily become overwhelmed in the details of formatting, and risk losing precious time in the writing process.

Finally, even if the authors do implement the guides to the best of their ability, they do not have any tools available to see if the document actually conforms to the formatting requirements. When it's time for the document to be sent downstream to the submissions team, formatting errors go along with the files, and the documents begin polluting the final submission timeline.

Raise the Bar of Quality

Armed with the knowledge that small changes to the authoring process can alleviate a huge bottleneck effect at the submission deadline, Senior Writers and Managers in the Medical and Technical Writing Communities can champion the process to Raise the Bar of Quality in their team reports.

The key point is to understand that there are ways to produce a better quality document without impeding the writing process. The new process begins with clear communication between Reg Ops and Medical Writing regarding the formatting guidelines. As this can be a very detailed, time-intensive process, organizations often look to consultants to orchestrate this activity. Consultants can assist by driving both regulatory and medical writing to define clear, concise guidelines for formatting that are consistent with global regulatory requirements.

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Additionally, consultants can advise clients on the industry best practices, and suggest enhancements that other clients have implemented. Merging the combined team requirements together forms the basis for the style guide, or offers improvements over the current style guide.

Ultimately, the true impact of the quality is measured after the electronic submission is in the hands of the reviewers. According to Sarah M. Connelly, MD, a Medical Officer for the Division of Antiviral Products, US FDA, the following aspects identify a high-quality eCTD submission:

- Organization
- Format
- Bookmarks
- Hyperlinks
- Dataset size
- Dataset definitions

The first four items in this list can be specified in a style guide. Organizational items include heading numbering, eCTD section numbering, tables, figures, and links. Formatting items include fonts, margins, spacing, pagination, styles, and properties.

Bookmarks and hyperlinks require a great deal of attention due to the high occurrence of broken, inactive, or external links found by the agency reviewers. Bookmark and hyperlink checks built into the authoring process catch and eliminate these errors early in the submission cycle.

The point in time of agency review is the worst possible time for these errors to be found, as an error-strewn, sloppy submission suggests that an organization cut corners to meet the deadline. On the other hand, a well-structured and consistently laid-out submission has a positive impact on the overall perception that the regulatory authority has for an organization. Attention to detail and adherence to style guide requirements indicate a high level of overall care and quality on behalf of the sponsors.

Value of Automation

The next step is to leverage the style guide within the authoring process by deploying to internal authors, external authors, and CROs for use. There is intrinsic value in creating automation for these quality checking processes to drive time savings, quality improvements, and reduced risks at the authoring, submission, and review levels.

When authors are given the ability to perform automatic formatting checks, it reduces the time it takes for manual cleanup. For example, by running a procedure to ensure consistency in fonts and heading numbering, the author is either assured that the styles and numbering are accurate, or they can further leverage automation to quickly navigate to and fix the problem areas.

Reg Ops can quickly and easily run the same quality checks to verify that the style guide was followed, and then proceed to rendering with a high degree of certainty that the document will render successfully. Finally, the time it takes the agency to review is reduced, because the submission is clean and flows efficiently. Quality improvements have long-range effects, even outside of the current application. Often times, a document or study report is used in multiple applications around the world. Enhancing and verifying the quality at the front-end of the process provides a clean document for use worldwide at any time for additional regulatory needs.

Clearly, a company reduces its risk for adverse review scenarios when submitting properly formatted data. The US FDA recently issued a draft document entitled, "Specifications for eCTD Validation Criteria." This document delineates problematic data issues, which have historically caused problems within the agency reviewing system. Known problems are documented in the specification, and range from password-protected files to invalid eCTD Leaf files. The specification classifies errors into categories of low, medium, or high severity. The severity levels outline the impact on the official receipt of a submission.

The document states:

Severity	Description
High	The error is a serious technical error, which prevents the processing of the submission and requires resubmission. The submission is considered not received by FDA.
Medium	The error may impact the reviewability of the submission but cannot be determined without further inspection by the review staff. The submission might be considered received by FDA.
Low	The error is a technical error, which may or may not impact the reviewability or the integrity of the submission. The submission is likely to be considered received by FDA.

Table 1 – eCTD Validation Criteria—Severity Levels

It is interesting to note that of the 126 draft error codes, 22% can be completely avoided by establishing proper document formatting and implementing early quality check processes at the PDF and PDF property levels, and by validating bookmarks and hyperlinks. Automation of the quality checking process can be accomplished with a homegrown solution or with the introduction of a third-party vendor. Although a homegrown process may sound like a quick route, a third-party vendor has the advantage of reducing maintenance and enhancement costs. Additionally, a vendor that is Microsoft Gold Certified can minimize Word integration and migration issues.

Making Quality a Priority

It is important to Reg Ops for the authors to follow the established guidelines of the style guides to enhance the overall quality of the submission. This allows the submission data to attain a high degree of readability for the agency reviewers, thereby reducing the overall review time. When the guidelines are not followed, the submission quality deteriorates, and formatting issues affect the PDF rendering in the electronic submission publishing tools, as well as add unnecessary overtime costs to the end of the process.

Consequently, if the formatting rules are not applied upstream at the point of authoring, the quality checks become a manual process downstream, which poses a risk to the timely completion of the dossier. An organization that places quality as a first priority augments existing processes to support such initiatives. Implementing phases of automation elicits a process change, and the savings can be measured in time, money, and resources.

Empowering authors with the tools to contribute to the overall quality process makes it intuitively easier for them to comply with rules they do not otherwise have time to consider. Empowered authors thereby reduce the risk of delays in the late stages of the submission.

Start with the Optimal Environment

Raising the bar for document quality can clearly be achieved by starting with the best possible environment. Reg Ops and Submissions groups have a vested interest in providing an optimal environment for the Medical and Technical Writers. Additionally, a similar solution could be provided to external authors, whereby they are enabled to produce quality documents within an automated environment. Likewise, all documents have the potential to undergo a quality check phase once this environment is in place, regardless of where the document was authored. Reg Ops, equipped with an understanding of how to provide this quality check environment upstream into the authoring group, can begin the process of raising the bar of quality. The resulting collaborative effort between the authoring communities and the Reg Ops teams leads to a high-quality submission for the organization. A well-formatted submission, in turn, leads to a more efficient review cycle for the respective agencies.

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LITERA

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