Getting Regulatory Submissions Right the First Time

Veeva

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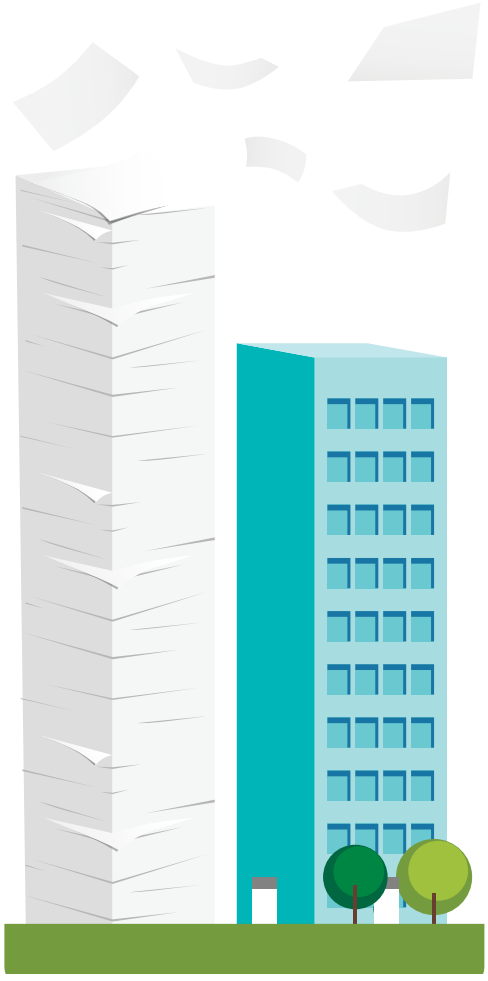
Regulatory submissions publishing has always been business-critical, but for years it was perceived as low value. As more companies emphasize the need to reduce rework and workplace stress, end-to-end approaches can help significantly accelerate submission publishing times.

Introduction

The industry has traditionally seen submission publishing as a nonstrategic, low-value function. But a poorly written and organized application with weak messaging and broken links can delay the approval of a new therapy just as readily, and for just as long, as incomplete product safety or efficacy data.

Regulatory approval delays and the need for strong, consistent messaging across corporate product dossiers are driving efforts and innovation to get good, well-written regulatory submission documentation right the first time. As technology advances, and continuous, end-to-end publishing applications[1] enable new ways to collaborate, more business leaders have begun to view submission publishing as another opportunity to optimize a business-critical function that deserves an automated, process-focused approach.

This ebook highlights some of the benefits of adopting a unified RIM solution that enables regulatory teams to plan, author, and publish submissions on a single, cloud-based platform. It also presents general change-management issues to consider, as well as real-world examples of improvements that companies have achieved by adopting end-to-end publishing approaches.



Improving a complex and stressful process

The process for submitting applications for new drugs and biologics in the U.S. and throughout the EU has come a long way in a relatively short time. Twenty years ago, application documents were managed entirely on paper and shipped by truckload. They were often lost during the shipping process, resulting in security leaks and approval delays.

The electronic Common Technical Document (eCTD), now **required** by many global Health Authorities, and improved document management approaches have reduced formatting and editing drudgery, but the size, scope and complexity of a typical application remain as daunting as ever. The typical NDA, for instance, runs more than a million pages, which – stacked on each other – would reach 24 stories, higher than most

[1] Lawrie, J., "How Continuous Publishing Speeds Regulatory Submissions," *DIA Global Forum*, February 2019.
[2] Gassman, C., "The Expanding Role of Regulatory Operations," *RAPS Regulatory Focus*, July, 2016, posted on veeva.com.

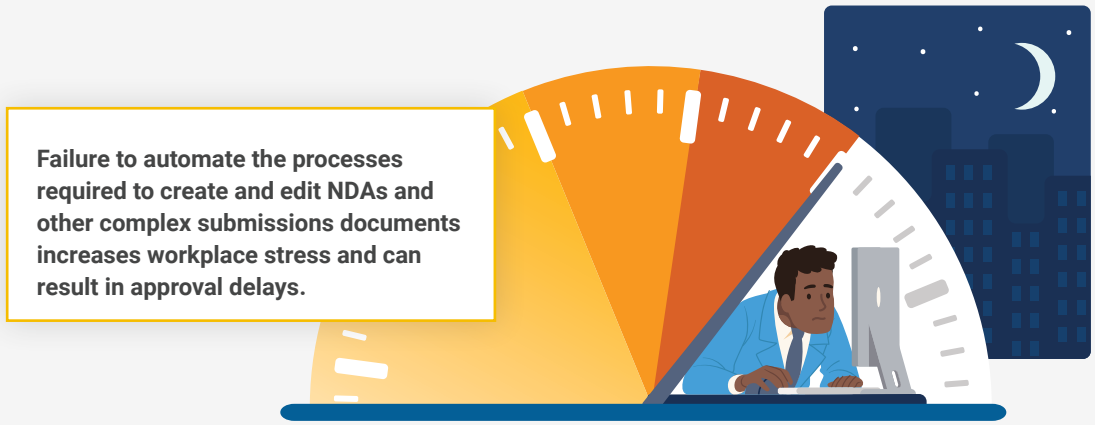
first-generation skyscrapers.[2]

Regulators respond to content and formatting deficiencies in these applications by issuing refusals to file (RTFs), which postpone review until sponsors correct underlying problems. Between January 2008 and December 2017, content and formatting problems contributed to more than 15% of the reasons that FDA reviewers gave for issuing RTFs[3].

From 2001 to 2018, one study[4] found formatting problems were responsible for 34% of the RTFs that FDA sent to sponsors, each of which delayed drug approval by an average of 17 months. Considering that each approval delay can cost sponsors $1-13 million per day[5] — and result not only in lost revenues, but in negative publicity and lower stock value — the impact can be significant.

And these figures don't even consider the less tangible effects that inadequate applications have on time- and resource-strapped regulatory reviewers and internal publishing teams. The cost of wasting reviewers' time only adds to the impact that repetitive, error-prone, and time-consuming manual processes and rework can have on publishing teams.

Given traditional work processes and technology and inflexible submissions deadlines, publishing team efforts are often concentrated at the very end of the development cycle, creating a serious time crunch. As delivery dates approach, the time available for handovers between author and publishers shrinks, while the effort required to finish the work increases significantly, especially when rework is required.



[3] Chahal, H.S., Mukherjee, S., Sigelman, J et al., "Contents of US FDA Refuse-to-File Letters," *JAMA Internal Medicine*, 181(4) pp 522-529, February 15, 2021.
[4] Shin, R, Im, J.,and Major, J., "Trends in RTF Actions from FDA and Impact on Drug Development," a joint poster presentation by Rutgers State University of New Jersey and Merck and Co., 2019.
[5] $1-13 Million per Day at Risk From Product Launch Delays, *PharmaLetter*, March 22, 2004.

Problems with traditional approaches

Traditionally, publishing has required a document management system; separate applications or vendors for the actual publishing, sharing, and viewing of files; and various internal spreadsheets for planning and tracking, as well as viewing and archiving systems. During internal submissions publishing review and approval, many documents are uploaded, then downloaded after they've been published.

Users typically review each submission document individually and send questions or comments on the evolving submission via email, a lengthy process that requires close coordination and attention to detail. They typically wait until a section or module has been completed, resulting in time lost before authors can review and approve hyperlinking and other critical content.

The resulting file is then transferred to a publishing program but cannot be reviewed until it has been moved to a submission validation tool. At that point, any errors must be corrected, and the resulting document is re-sent to the publishing program and validation system. For an NDA, this cycle may be repeated several times.

Existing approaches have created challenges and frustrations, for both regulatory authoring and publishing teams. Authoring teams are often inexperienced with formatting and uncertain about what messaging and keywords to use, and their key word and navigational strategies may be inconsistent, both within the same sections and between different functions, such as quality or safety. This inconsistency can annoy regulatory reviewers, who may find the submission difficult to review.

Publishers, meanwhile, face the following challenges:

Ensuring consistent linking and navigational strategies, and addressing problems with the company's keyword link database and lack of best practices for using it

Reducing publishing rework

Maintaining a consistent voice and strong company position across the product dossier

Working under pressure and within aggressive timeframes to ensure on-time submission

That last point requires familiarity with the needs of both internal and external publishing stakeholders. At many companies today, documentation that is crucial to the company's dossier is handed off to publishing teams very late in the cycle, resulting in content being locked late, often dangerously close to the target submission date. Late changes to content-locked documentation pose

validation issues as publishers rush documentation rework, and deal with multiple vendors and CROs that only complicate the process. This is especially true for teams who aren't dealing with one submission at a time, but multiple submissions at once.

This vicious cycle of ad hoc content creation, segregated publishing processes, and lack of data access only exacerbates the risk of errors and costly approval delays. If authoring and publishing teams are not working in sync, publishing teams have less time to complete revisions and rework files and may need to recruit external contractors to finish the work in time. These contractors will need to be trained, further increasing the risk of error and noncompliance. In addition, regulators may ask follow up questions after they first receive the documents, forcing teams to consider and correct problems that might have been avoided by having real-time access to more data and more automated workflows.

How continuous approaches reduce RTFs and rework

More companies are turning to continuous processes for submissions publishing to eliminate rework and problems that can lead to RTF-based approval delays (Box). Part of unified regulatory information management (RIM) systems, these solutions enable regulatory teams to shorten publishing timelines, improve efficiencies, and connect publishing more closely with broader development efforts.

Working on a single platform, regulatory authoring and publishing teams end up with one final submission application document that incorporates all prior comments and corrections, instead of a succession of iterative versions, each of which requires additional changes. This approach makes it easier for users to identify sources of documentation and formatting problems and issues with source content links and PDF navigation. These improvements not only eliminate rework but enable continuous improvement and enhance collaboration between the teams. They also ease development of consistent company messaging across all submissions, which can improve reviewers' opinion of the company.

With the right RIM system in place, teams can find and address potential errors and warnings such as broken links to source data in real time as the submission evolves, instead of having to wait until the document has gone through the latest republishing and revalidation cycle.

Top benefits of continuous publishing

- ✔ End-to-end document management on a single system
- ✔ Elimination of manual tracking
- ✔ Access to the right document version at the right time
- ✔ Automated content development
- ✔ The ability to complete key publishing steps during authoring
- ✔ Improved navigation from re-using hyperlinks across studies

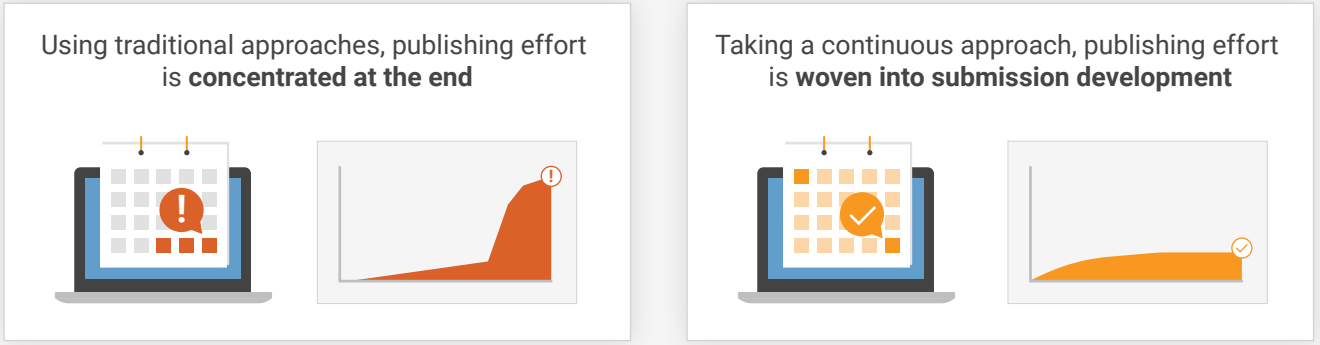
Submission publishing software tags each submission with identifiers that establish a trace based on location, submission type, key dates, and other unique information. It has also been designed to allow information that doesn't exist at the earliest stages of development to be added later. This enables content plans, for example, to include links to existing documents as well as to documents that are planned but do not yet exist.

Instead of working on issues during the publishing stage, teams who use these tools benefit from being able to:

- Manage PDF navigation aids and bookmarks earlier, during content creation
- Leverage automated processes to test hyperlinks and to compile and validate files
- Track processes and workflow in real time to maximize transparency
- Match document structures automatically to whatever outline is needed for the type of submission application involved.

One of the most visible improvements seen with continuous publishing is eliminating the last-minute QC editing and formatting crunches that result from traditional approaches by allowing teams to distribute their efforts and collaborate more closely throughout the product development cycle (**Figure 1**). The continuous approach also eliminates the need for publishing teams to put in long hours at night and on weekends to meet deadlines, offering improved work/life balance.

FIGURE 1. DISTRIBUTING EFFORTS THROUGHOUT DEVELOPMENT

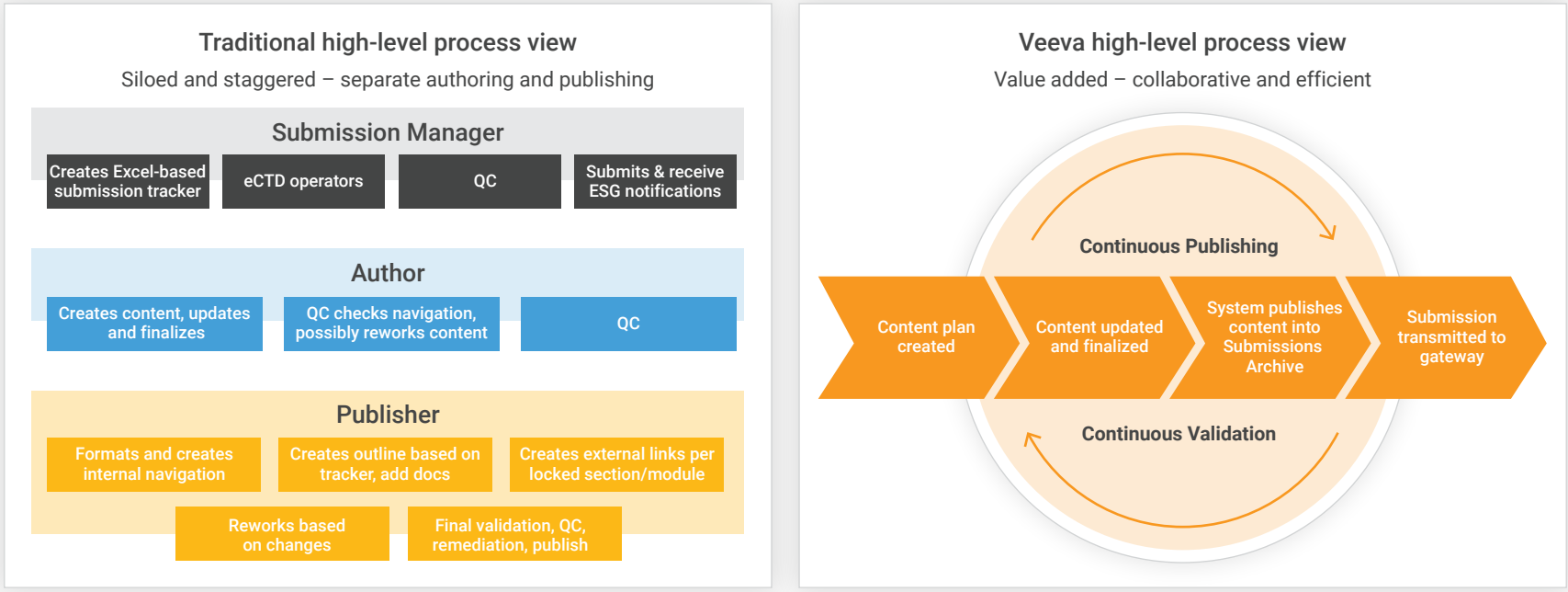


Traditional approaches require serial document reviews by individual team members, and use disconnected processes, systems, and tools. Much time is wasted on waiting — for documents; for people to perform tasks before the publisher or author can complete their assigned tasks; for team members to review hyperlinks.

If the information doesn't come in on time, some team members will have to work longer hours and cancel planned vacations. In contrast, end-to-end continuous publishing allows teams to create, review, revise, and validate documents continuously and in parallel throughout the development cycle.

This way, teams can identify content, publishing, and validation issues in real time, as they occur, rather than having to wait until the latest round of document publishing and validation to correct them. Bringing teams together and allowing them to work with the document in real time, as it evolves, can halve the time between planning and submission (**Figure 2**).

FIGURE 2. ELIMINATING TRADITIONAL SILOS AND DISCONNECTS



At a growing number of companies, teams are quantifying the time spent and taking steps to cut down on those hours. End-to-end publishing, within the context of a RIM system, enables teams to reduce rework, and the time they once wasted correcting repeat problems, by allowing them to access the right information at the right time.

For best results, get advice from cross-functional user teams

Ideally, RIM-enabled publishing requires a foundation for managing and archiving submissions. For new submission publishing projects, users should establish cross-functional teams that include authors, submission leads, and publishers – and involve contract partners and vendors – to guide document planning in the new system from the earliest stages.

> *The ability to work with the document in real time, as it evolves, can halve the time between planning and submission.*

For optimal results, team members should be committed to authoring, reviewing, and approving submission documents in RIM using good data-management practices. But equally important are an openness and commitment to change the traditional interaction between regulatory authoring
and publishing teams, and to shift from an operational to a tactical mindset.

Sponsors that outsource publishing should not be afraid to challenge CROs to come up with more tactical approaches or assume that their use will cost more. Be sure that contractors receive training as thorough as that provided to in-house staff.

Real-world benefits at Moderna, Melinta, and Dermavant

Using a new health authority querying tool within Vault RIM, **Moderna** was able to streamline publishing timeframes at a time when submissions had increased 15-fold.[6] Now, unified data and documents allow its submissions publishing teams to filter through more than 1,600 queries and answers and zero in on the most relevant responses, along with the full text of each correspondence file. This approach not only increases response efficiency but improves the consistency of information sent to regulators.

The company can also assign and track response progress via a Health Authority question object in Vault RIM to assign and track progress in responses and enable internal and external experts to collaborate on responses and ensure their completeness

[6] Veeva Systems, "Moderna Improves HA Query Management with Veeva Vault RIM" *Veeva.com*, 2021.

and accuracy.

Melinta Therapeutics adopted Veeva's Vault RIM Suite and Vault Submissions Publishing and was able to cut the average submission time in half, allowing its regulatory team to publish 100 submissions within two months of implementation.

The clinical-stage biopharmaceutical company Dermavant Sciences also turned to RIM-enabled Vault Submissions Publishing to integrate publishing into day-to-day product development. The company had been using traditional publishing tools and a time-consuming process that required files to be transferred numerous times between sponsor and contractors. Dermavant planned to be first-to-market with a new treatment for plaque psoriasis and needed to streamline processes.[7]

The company had already implemented the Veeva Vault RIM Suite, and its regulatory team activated Vault Submissions, Submissions Archive, and Submissions Publishing, starting with a basic framework, and incorporating its own processes and preferences.

Input from content authoring provided insights into existing inefficiencies and rework, which resulted in use of gated workflows. The team decided to use Vault Submissions Publishing for the new product's NDA, and implemented the application in six weeks, moving traditional QC and copyediting upstream during content creation.

The new system improved transparency by enabling team members to see how documents were shaping up as development progressed, allowing them to identify and fix problems much earlier in the process. The content development team was able to add live links to source documents and link those to other documents in Vault.

Ultimately, the project reduced Dermavant's NDA publishing timeline by one month and allowed the publishing team to meet its deadline six weeks ahead of time. Users reported experiencing less stress, better work/life balance, and having more confidence in the new system.

By addressing the very real needs of submissions publishing teams, these new approaches will help the industry accelerate publishing timelines and ultimately get treatments to patients faster.

Read here for more information on Veeva's end-to-end Vault Submissions Publishing solutions.

[7] Veeva Systems, "Dermavant Shaves Weeks Off its NDA Timeline", *Veeva.com*, 2021.