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WHITEPAPER

FIVE SECRETS OF GREAT PUBLISHERS

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Adair has 15 years of experience in Regulatory Affairs and has worked for companies such as ImClone Systems and Celgene where she led the planning, review, and delivery of high-quality regulatory submission dossiers in support of the development and registration of anti-cancer compounds worldwide.

At PharmaLex Adair leads a team of Regulatory Operations professionals and is accountable for the overall planning and management of Regulatory Operations resources to effectively support timely and quality submissions to Health Authorities (i.e., FDA, Canada, etc.).

Introduction

The FDA's mandate for life science companies and manufacturers to submit information in electronic format has solidified the Regulatory Publisher's function as being essential to the drug development process. Daily tasks have shifted from clerical work such as printing, photocopying, creating tabs, and page stamping to a new set of technical skills including electronic document processing and management (to put it simply), systems expertise, project management, and critical problem solving.

The title Regulatory Publisher is not completely standardized across the industry - varying from eSubmissions or eCTD Specialist to Regulatory Operations Associate. The role varies depending on the company size – publishers are often somewhat overlapped with the IT function and are expected to validate software and administer tracking, publishing, validation, and document management systems. In addition, they may plan and manage large complex submission projects.

Companies now typically require publishers to have at least a bachelor's degree, knowledge of eCTD guidance and regulations, and 2-3 years of experience with eCTD, eDMS, and Regulatory Information Management (RIM) software.

As the role of the Regulatory Publisher is evolving one might ask what distinguishes a good publisher from a great one? Here are five secrets that make the difference:

Secret One: They know the Regulatory Affairs domain.

A Regulatory Publisher who possesses a basic understanding of regulatory affairs and the drug development process is enabled to know "what makes sense" within the context of a given submission and therefore is already ahead of his peers. Through this knowledge he or she knows particular details that may improve the quality of the submission. He or she would know that a Sponsor should never submit a supplement to an IND or an amendment to an approved NDA; and the correct forms to include per submission type (i.e., 356h/eAF with marketing applications for U.S. and E.U respectively and 1571 with INDs). His or her focus lies on presenting information in an organized format; understanding the exact details of the content is ancillary. A great publisher will detect any missing or misplaced information – for example, inclusion of a document to reference without a link to the document, leaving the reviewer to wonder about its relevance.

"A great publisher will detect any missing or misplaced information."

Secret Two: They have a network.

Great Regulatory Publishers recognize that they are part of a Regulatory Operations service group. They exist to support the organization in submitting high-quality and timely information to Health Authorities. Looking up a regulation or guidance document quickly is a common task. It is judicious to be familiar with regulatory message boards and keep up to date on ever expanding regulations. Having a network of other publishers to consult with when in need is also beneficial. A great publisher maintains good relationships with vendors/partners/health authorities and has contacts in Clinical Operations, Medical Writing, CMC/Technical Writers, Marketing, Quality Assurance, Legal, Analytical, Manufacturing, and of course Regulatory Affairs. On the final sprint towards an important submission deadline, when timelines are tight and stress levels are high, a resilient personal connection to all stakeholders is key. Furthermore, knowing and using the organization's systems including RIM, eCTD, eTMF, QMS, eDMS, etc. is necessary. It is important to utilize tools such as Submission Trackers (the "Bill of Materials" for a submission) and issue trackers to always know the status of the documents and submissions one is working on.

Secret Three: They think ahead.

There are a ton of tiny steps and checks that publishers perform on a daily basis. Great publishers don't leave an opportunity for error, but instead follow a pre-defined process and prepare as much as possible ahead of time to limit the steps on the critical path.

Source Documents

Having a checklist for source document QC to ensure that documents are actually "submission ready" and that errors are resolved early in the process will spare a publisher from having to do re-work later on. Note: Re-work is a major cause for submission delays. Fixing document errors shortly before the submission deadline is more costly than fixing them early in the process.

There are tools on the market that support the publisher to check source documents. In the worst case, he or she will have to scroll through them and do a manual check. This is a time consuming but crucial task as it prevents the need for any last minute fixes. Some important things to check in source documents include blank pages, incorrect document headers, sufficient margins, continuous pagination that matches the electronic pdf numbering, correct granularity, standard fonts that are 9 pt. or higher, that a table of contents is included for documents longer than 4 pages, references/attachments have been provided, numbering and legibility of tables/figures, etc.

Bookmarking and Hyperlinking

After the publisher has performed the source document QC, he or she will begin to "publish" the documents according to the pdf specifications and applicable guidance documents. A publishing manual provides guidance on what to check and fix (where appropriate) including the pdf filename, the document properties (description, security, fonts, initial view, etc.), the page size, and page orientation.

Additional checks are performed to make sure the bookmarks (at the very least) match the table of contents, do not contain spelling errors, are nested correctly, go to the correct destination, and are set to view in inherit zoom.

Hyperlinks will be checked to make sure they are displayed as blue text, go to the correct location, and are set to view in inherit zoom. A great publisher will go the extra mile and search for words such as section, table, appendix, figure, refer, see, etc. to ensure that no links were missed. Documents will be checked to make sure external hyperlinks to URLs were deleted and that links are relative and not absolute. Note: Documents should be final at this stage. Any changes to the content, any versioning of the files will result in publishing re-work.

Final Published Output

Once the publisher compiles the submission in the applicable eCTD tool and the XML has been generated, publishers will open the submission in an eCTD viewer and review the leaf titles, lifecycle operations and folders. He or she will also check metadata such as applicant name, application number, submission date, product names, sequence number, submission type, application type, and related sequence number in the Regional XML. Great publishers will check the attributes/metadata to make sure they were entered exactly the same as before, down to spaces, dashes, periods, capitalization, misspellings, etc., so that new folders/sections are not created. They'll review the documents to ensure that every document is included in the correct place in the submission. STF study titles, IDs, attributes, and tags will also be checked for U.S. specific submissions.

Last (but certainly not least), publishers will run the submission through an eCTD validator to double check that nothing was missed. It's also recommended that the Regulatory expert involved in the submission does a high-level check to make sure everything appears as expected. Note: there should be no changes unless absolutely necessary at this point!

Secret Four: They see the forest AND the trees.

It's important for publishers to understand the impact that her/his work has in the greater context of the company. Understanding the bigger picture and long-term goals of the company you are working with is fundamental for each submission. Factors such as commitments to Health Agencies, beating a competitor to market, commitment to stockholders, and most importantly the aim of bettering someone's life (or saving it) can affect timelines and influence the submission accordingly. For example, if the application you are working on is for a rare pediatric disease, the company may be able to receive a "priority review voucher" that allows them to fast-track the drug application.

Secret Five: They make decisions.

Great Publishers are able to perform risk assessments to mitigate errors and rework later in the process as well as provide solutions to issues that arise. Often it's a decision between time and quality, i.e. fixing the error, but missing the deadline OR meeting the deadline, but submitting with minor issues. Great Publishers understand the impact of either decision and know their flexibility in decision-making. If they can't make the call themselves, they should know the escalation pathway.

- **Scenario 1:** Publisher finds a mistake in a document shortly before the submission deadline.
  Assessment: What is the risk of NOT fixing the mistake? What is the impact?
  If the mistake is in the capitalization in a bookmark, it may not be worth fixing this late in the game. However, if the mistake is in a number in the document (50 mg vs. 5 mg), it probably needs to be fixed (especially if there will still be time to do the fix and have the submission out in time).

- **Scenario 2:** Submission is final and ready to be sent out. The publisher runs one last eCTD validation and receives 2 high errors.
  Assessment: What is the risk of NOT fixing the mistake? What is the impact?
  In this scenario, the submission is likely to be rejected due to technical aspects so the publisher is left with only one logical decision - the fix is very important as the submission is not considered "received" by the Agency until it goes through the various checks. The publisher will have to take appropriate actions.

Conclusion

The role of Regulatory Operations has changed drastically over the past years and with it, a change in the knowledge and experience required for Regulatory Operations publishers/associates.

Whether you are a publisher looking to grow, or a manager looking for talent, there are certain qualities Great Publishers should possess: know the Regulatory Affairs domain, have and maintain a network, think ahead, keep in mind the larger vision and goals of the company, perform risk assessments and make calculated decisions.

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