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TOPICAL FEATURE

Preventing Chaos: The Critical Role of the Submission Lead

Anjana Bose, PhD; Mark Bowlby, PhD; Brenda Taylor, MS, CAPM; Steve Sibley, MS / Certara, Inc, Radnor, PA

ABSTRACT

Pharmaceutical product marketing applications represent the end result of years of development, significant financial investment, months of work, and the collaboration of a very large cross-functional team. Clearly, the Submission Lead for any marketing application team is a critical role. Experienced regulatory/medical writers often have the necessary array of skills to make excellent Submission Leads, whether they are overseeing only the writing activities or leading the entire submission team.

The Submission Lead serves as the "connector" by providing strategic and tactical oversight throughout the process to ensure on-time preparation of high-quality documents. By enabling the work in each stage of the submission, from initial regulatory submission strategy through publishing and submission, the Submission Lead ensures the development of a comprehensive and cohesive marketing application. Submission Leads wear many hats and ensure that the team is functioning well and communicating at all times. Teams benefit from a Submission Lead with extensive marketing application experience because they are better able to mitigate the challenges and risks that arise.

Submission Leads fluent in the strategy and content of the submission are able to drive discussions and prioritize team activities. Most importantly, as the project progresses, this strategy and content knowledge allows the Submission Lead to recognize potential cross functional impacts of each new development and to ensure the necessary parties are brought together to address those impacts. Like any large team effort, a clearly defined lead role and agreed processes are critical to achieve a high-quality, on-time marketing application that is accepted for review and ultimately results in regulatory approval.

Regulatory submissions are complex, and each has its own unique characteristics and challenges. New regulatory guidelines across regions and new innovative therapies and digital tools have added even more complexities that require dynamic planning, close coordination, and effective project management.

Marketing applications can take many forms, from initial applications for first-time marketing of a product and supplemental submissions to expand indications or dosage forms to generic or biosimilar applications. All require input from a broad, cross-functional team and inclusion of a large and diverse collection of source data and reports supporting the proposed product and its labeling to successfully gain approval. A successful, high-quality marketing application requires a well-balanced team comprising individuals from regulatory; commercial; chemistry, manufacturing, and controls; nonclinical; clinical; medical; statistic; programming; data management; safety; medical writing; and other fields. With so many individuals and areas of expertise involved, communication becomes critical.

Key to successful submission team functioning and delivering is a clearly identified overall lead (ie, the Submission Lead) and a lead for each function. These roles oversee and manage the team of individuals within their oversight area; ensure the open flow of communication to, from, and within that oversight area; and serve as the primary point of contact for that area. In our experience, regulatory/medical writers with submission experience are well suited to the Submission Lead role, whether overseeing all writing activities or leading the entire submission team. We attribute this to the fact that each regulatory/medical writer must interact with a broad range of functions to develop and deliver a document, be a good communicator, and establish and adhere to an agreed set of timelines. In addition, each regulatory/medical writer works in depth with both the underlying source data as well as high-level messaging, interpretation, and presentation.

THE SUBMISSION LEAD ROLE

The Submission Lead plays a key role in coordinating submission teams, both internally and externally. The Submission Lead reaches out to team members for information and status updates, conducts regular meetings to keep everyone

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informed, and establishes appropriate contacts with outsourced vendors for timely exchange of information.

Furthermore, the Submission Lead, in conjunction with the Regulatory Lead,

- guides the team in developing a comprehensive electronic common technical document (eCTD) content plan and strategy;
- integrates perspectives of various functional areas, contributors, and subject matter experts into cohesive messaging to meet regulatory requirements per the eCTD;
- communicates expectations of regulatory reviewers to ensure that these are factored into the various summaries and reports;
- assists in authoring and reviewing documents to ensure consistency in messaging and adherence to regulatory guidelines for the product label; and
- identifies and monitors potential risks to the submission, working with the team to develop contingency and risk mitigation plans throughout the submission process.

Expanding upon basic skills required for authoring or leading a single document, leading a submission requires extensive project management skills as well as consultant-level submission expertise. Effective and relentless timely communication with all parties is vital, as is flexibility, securing consensus for any changes, and resolving issues as they arise. A Submission Lead serves as the "connector" by providing strategic and tactical oversight throughout the process to ensure on-time preparation of high-quality documents.

THE SUBMISSION LEAD'S ROLE IN ENABLING THE WORK THROUGHOUT THE 5 STAGES OF A MARKETING APPLICATION

Embarking on a marketing application requires extensive planning and is carried out in stages (Figure 1).

Stage 1: Regulatory Submission Strategy

The submission team (ie, Submission Lead and core team members) should be formed 9 to 12 months before the planned submission date to establish the overall goals and strategy for the submission at this stage, including the development of key messaging, target product profile [TPP], and plans for interactions with relevant regulatory authorities. To ensure confidence in the proposed strategy and plans, the Submission Lead or Regulatory Lead should review all previous interactions with the regulatory agencies, focusing on prior agreements and how they have been addressed. Standard of care and recent approvals for similar products and for any products in the proposed indication must also be identified and made available to the team.

Team meetings are initiated at this stage, starting with a formal kickoff meeting to ensure alignment on the goals and expectations for the submission, to review a high-level timeline, and to define roles and responsibilities. The Submission Lead should also establish a regular cadence of team meetings to begin following the kickoff meeting, perhaps monthly or biweekly and increasing in frequency to weekly closer to the planned submission date.

Key messages, which serve as guideposts for all content development, are important for the submission and labeling. There are many ways to approach this. Many sponsors use "storyboards," TPPs, draft labeling, a core data sheet, or other documents as tools for building and capturing key messaging. A significant pitfall with these approaches that the Submission Lead must watch for is that these key messages are often aspirational and disconnected from data. In addition, these internal documents can become formal documents that require time, effort, and prioritization from key team members and distract the team from preparation of the actual submission documents.

Presubmission meetings with regulatory agencies are also critical for successful submissions and are a key part of the Submission Lead's strategic input early in the project. For example, for US Food and Drug Administration (FDA) submissions, a key consideration is the option for an initial Type C FDA meeting to address pooling strategy, data set inclusion, and other submission plans. These meetings typically occur at least 6 months before the planned submission date. For submissions to multiple countries, a presubmission meeting with each country is necessary. This can greatly complicate planning and strategy as the timing of each meeting and each planned submission date must be accounted for in the timelines. More importantly, the

Figure 1. Marketing application development stages.

timeline and the content development of the documents must consider the potential for each country's regulatory authority to raise different (and sometimes conflicting) questions and requests during presubmission meetings. Presubmission meetings for marketing applications also typically require at least topline data from the final Phase III clinical trials and submission of a briefing document at least 1 month before the meeting. Therefore, the timing of these activities must be built into timelines as they may be on the critical path for completing drafts of key documents.

Stage 2: Timeline and Content Planning

The submission timeline must be sufficiently detailed to confidently identify and track the critical path items. The content plan, which should account for timelines as well as for every file in the submission (including datasets, case report forms, analytical method reports, etc) is a critical living tracker and is reviewed with the team throughout the entire submission process. It is closely tracked by the publishing team to ensure each element is placed in the appropriate eCTD folder per regulatory requirements. Although maintaining the timelines and content plan may fall to different functions (eg, Project Management), the Submission Lead makes certain that all groups have a voice and a seat at the table and that every activity and deliverable has been taken into account.

Successful content planning and timeline development are largely dependent on knowing and identifying dependencies within and across modules. These dependencies range from the obvious (eg, study reports being dependent on final data and summary documents being dependent on well drafted study reports) to the more nuanced (eg, availability of finalized chemistry, manufacturing, and controls [CMC] stability data, nonclinical SEND datasets, or a population pharmacokinetic and exposure-response report). Ideally, the timeline and content plan are comprehensive, and the team has considered some alternate scenarios based on unexpected data outcomes, study completion delays, and regulatory authority feedback. This is a continuous process of maintaining an agreed plan and adjusting and incorporating new developments as they arise.

Stage 3: Content Development

"Storyboards," the TPP, the draft labeling, a core data sheet, or other documents serve as the source for key messaging and a reference and guide for all content development. The Submission Lead enables authoring of submission documents by championing use of a system for coauthoring and subject-matter expert review. By maintaining familiarity with the data and reviewing documents for consistent messaging and presentation across the submission, the Submission Lead is able to advise and guide the writers and team. Throughout the process, Submission Leads may also guide writers on consistency of messaging and presentation, how to adjudicate difficult comments, assist writers with comment resolution meetings, and manage any conflict resolution on complex issues.

Since the advent of the CTD format, content is organized in a modular structure (ie, Modules 1 through 5). This structure simplifies and standardizes submissions but also requires transparency among disciplines, so appropriate cross references are included to locations with more detailed information. The Submission Lead is integral to enabling this transparency. In addition, successful development of each document requires comprehensive identification and agreement on the source data and documents to be used and referenced as well as when these documents and references will be available. Best practice is for the writer to generate a shell or prototype version of the document for team review to establish the overall structure and flow of the document as well as to confirm agreement on the sources to be addressed before attempting to author the first full draft of the document.

Stage 4: Content Finalization

In collaboration with the functional areas, the Submission Lead ensures that the lists of reviewers and approvers are proactively defined and agreed upon per the sponsor's existing processes and governance. Before any reviews, the Submission Lead provides reviewers with best review practices training. As part of the development of the overall submission timeline, the Submission Lead or a delegate schedules reviews, comment resolution meetings, and approvals. Critical to the success of these reviews and approvals is ensuring that approvers and any other external-party or upper-management reviewers are included as early as possible in the process. Approvers, external parties, and management seeing the document for the first time at approval is a recipe for disaster, regardless of the quality of their input.

Stage 5: Publishing

The Submission Lead plans for submission-level publishing in accordance with the content plan when developing the full submission timeline. Working with Project Management and Regulatory Operations, the Submission Lead ensures the content plan is being used to track document publishing status, missing components, and final review and approval of the published submission. It is especially important to ensure that all the supporting documents (eg, report appendices) are included and can be linked. Although these steps will always be the final steps in the process and are therefore rate-limiting to the submission, planning for these

end-of-submission steps from the very beginning is key. The Submission Lead ensures the whole team has visibility of the time required for these activities and that documents are being published as soon as they become available.

RISKS AND MITIGATIONS

All submissions will encounter roadblocks, even with perfect, comprehensive planning. The key to a successful submission is anticipation of the risks and creation of an action plan to mitigate those risks. Often, this is done at the initial stage of planning by listing potential risks so that an appropriate contingency plan can be developed. The risks and mitigations associated with marketing submissions include

- ***Poor communication***
  Clear, open communication across the broad team is key to success and usually accomplished via weekly submission team meetings with an agenda provided to the team before the meeting, minutes, an action items log, a detailed timeline with dashboard, and a content plan. This is especially true for sponsors and their vendors but also for core teams that enable decision-making. Personality challenges/conflicts can always arise, so having standards of conduct and escalation paths may be necessary.
- ***An incomplete or disconnected team***
  At a minimum, a lead representative from each functional area is needed to support a submission. It is critical for these leads to have the ability to communicate both with those outside their area of expertise and experts in their discipline. Team dynamics make a submission pleasant or painful, so team members need to work together, value input, and have time available to dedicate to the program. Inclusion of multiple sponsor companies and vendors can make this more challenging.
- ***A lack of clear roles and responsibilities***
  Clear roles and responsibilities must be established, often with a Responsible, Accountable, Consulted, Informed chart (commonly referred to as a "RACI") to define and assign roles. A balance between reviewing outside of your expertise and "staying in your lane" is important to success and efficiency.
- ***A lack of oversight or engagement***
  Establishing a submission governance structure and risk log are important, as is involving senior managers from relevant functions early on. Getting it right the first time and avoiding late, drastic changes in approach and messaging can be accomplished by including approvers in Draft 2 reviews or earlier. Detailed planning and early engagement with a core team containing the key functional areas is critical.
- ***Inexperienced team members***
  Mentoring of inexperienced team members is an often-overlooked component of the job of the Submission Lead. The best way to learn is by doing, and everyone has a first submission (or new role) and may need some guidance or oversight. The Submission Lead can directly guide or mentor others as well as find other experts to help do so as well. A clear sign of a healthy, high-functioning team is when less experienced team members are provided with the support they need.
- ***A timeline that is only high-level or incomplete***
  Developing and agreeing upon a realistic detailed timeline is important. The critical path must be clear, and each functional area must have visibility to more than just its own timelines. Timelines also are living documents that need to adapt with changing circumstances as problems develop in execution of the agreed timeline. The Submission Lead works with other team members to keep timelines up to date and ensure communication of any changes, and their ramifications, across the team.
- ***Poor budget and timeline management***
  Regardless of how many contract organizations are involved in a submission, budgets of funds or time allocated toward specific activities need to be tracked and adjusted as needed. Teams need to understand when additional requests for data analyses or extra document draft reviews will affect budgets and timelines and when they will not.
- ***Results that are not as anticipated***
  A priori contingency planning helps teams avoid derailment when results are not as expected, making it easier and quicker to select and implement alternative scenarios and adapt accordingly. The Submission Lead needs to drive the revisions and facilitate bringing the key team members together to address these changes and agree on the path forward.
- ***Teams panic in a crisis***
  When submission teams are stressed and overworked, tempers can flare, and details can be missed. It is perhaps the Submission Lead's most important responsibility to be the "calm in the storm" and move ahead, keeping everyone aligned and engaged during these times.

VALUE OF EXPERIENCE

Experience is the single most important skill necessary for a Submission Lead. Submission Leads get this experience by having had a key functional role within prior submissions. Most importantly, an individual who listens to and

learns from all of the submission team discussions—and not just those relevant to their function—will gain the experience necessary to lead the broader submission team. We believe the experience most needed for a Submission Lead is to have been through the submission process previously, including postsubmission regulatory defense through to approval. Why? Because that individual knows what the end looks like, what done looks like, and even what done *well* looks like. This enables the Submission Lead to provide the guidance and direction teams need as new issues arise, timelines shift, and the team struggles with critical periods of activity. Experience also enables the Submission Lead to strategically guide the team to a solid and detailed strategy, content plan, and timeline long before the actual submission work even starts. The Submission Lead has ideally faced these situations before; lived through various scenarios and solutions; and come out with a good sense of what works, what doesn't, and how to plan for and mitigate those inevitable pitfalls. Finally, the Submission Lead is in a position to keep the team focused and drive them to success. They do this by being focused; thinking in terms of scenarios; and ensuring the team is clear on their roles, responsibilities, actions, and agreed decisions.

DISCUSSION

Pharmaceutical product marketing applications represent the end result of years of development, significant financial investment, months of work, and the collaboration of a very large cross-functional team. These marketing applications are a significant milestone in any product's development. The Submission Lead of any marketing application team fulfills a critical role that requires a daunting array of skills, including interpersonal/communication; project management; extensive drug development, regulatory, and marketing application knowledge; and leadership. The Submission Lead is essential to enabling a submission team's work and addressing all of the challenges and risks that typically arise during development of a marketing application. Experienced regulatory/medical writers often have this array of skills and make excellent Submission Leads, whether overseeing only the writing activities or leading the entire submission team.

Every team needs a capable leader. Without a clearly identified and capable leader, miscommunication and chaos can ensue. Submission Leads must be accountable and responsible to the submission team. The Submission Lead wears many hats and ensures that the team is functioning well and communicating at all times. There is no such thing as overcommunication on a submission project; submission teams need to keep the information flowing flawlessly. Although this role can be challenging, there is a huge sense of pride and achievement that comes from successfully leading a high-quality submission that meets its deadline and ultimately results in approval.

Leading and working with large multidisciplinary teams under tight timelines with complex results and interpretations is difficult, even for seasoned Submission Leads. Increasingly, more than 1 sponsor company as well as multiple vendors are involved. In addition, contract research organizations delivering the clinical studies, and other vendors supporting nonclinical, CMC, statistical programming and analysis, and other key submission components each constitute supportive but crucial roles. The Submission Lead must ensure that roles and responsibilities are clear, that communication is flowing across these disparate organizations, and that all activities are being accurately tracked.

Although much of the role of a Submission Lead may overlap with project management and an experienced Project Manager is an essential part of any large submission team, it is most efficient for an individual who can speak to the data, deliverables, and messaging to serve in the Submission Lead role. A Submission Lead fluent in the strategy and content of the submission allows them to drive discussions and prioritize team activities. Most importantly, as the project progresses, this strategy and content knowledge allows them to recognize potential cross-functional impacts of each new development and ensure the necessary parties are brought together to address those impacts.

Author declaration and disclosures: *All authors are employees of Certara, Radnor, PA, USA and may own Certara stock or stock options.*

Author contact: *steve.sibley@certara.com*