



Editorial

The Regulatory Expert Seminar session at the 2021 Spring EMWA Conference took us on an amazing journey through marketing authorisation applications from a regulator's and medical writer's perspective. One of the presentations focussed on the challenges of accelerated reviews, assessments, and timelines from a regulatory affair's perspective, in the context of marketing authorisation submissions for COVID-19 vaccines.

Accelerated regulatory submissions have great impact also on medical writers' tasks and processes. In this article, Arthur Jarov guides us through the challenges of these submissions and shares with us valuable tips to prepare successful documents despite accelerated timelines.

Happy reading!

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Chair of the PV SIG

Accelerated regulatory submissions: Less haste, more speed!

Introduction

Accelerated regulatory submissions pose major challenges even to the most experienced medical writers. This article discusses those challenges and proposes practical ways of maintaining high document quality and consistency while meeting ambitious submission timelines.

Why the rush?

Writing a regulatory submission dossier is a major undertaking; it requires thousands of hours of work and usually takes several months. Typically, project teams need 4 months to deliver clinical documents such as the pivotal study Clinical Study Report (CSR) and high-level documents (HLDs), including the Common Technical Document (CTD) Module 2.7 summaries and Module 2.5, the Clinical Overview (CO). A Risk Management Plan (RMP) is also required when applying for a marketing authorisation in some regions and countries.

Although 4 months may seem a reasonable time to prepare those documents, most authoring teams find the experience stressful. The sheer volume of work – combined with challenges in data interpretation and document complexity – can be overwhelming for an inexperienced team. In the dossier, the applicant must not only present all available data on the

investigational product, but also provide a critical analysis of study designs, methodology, and results. Any proposed labelling claim must be justified and backed up by scientific and clinical evidence.

Analysis of clinical safety data presents particular challenges, especially for a new drug application. Safety data are described in detail in CSRs and summarised in the CTD Section 2.7.4, Summary of Clinical Safety (SCS), and the relevant sections of the CO and RMP. An

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important purpose of the evaluation of safety data is the evaluation of Adverse Drug Reactions (ADRs). Depending on the clinical development programme and the indication, safety data from several studies can be pooled to allow detection of less common ADRs. Although some applicants use programmatic methods for ADR detection, this process cannot be fully automated, as it requires careful review by safety physicians and risk management experts. Mistakes in ADR identification can have disastrous consequences for patients, healthcare professionals, and health authorities (HAs), not to mention the legal and financial consequences for the applicant. Therefore, this crucial process cannot be rushed.

Nevertheless, project teams often find themselves under pressure to accelerate submissions. Such pressure can come from company management, HAs, or both. In the United States,

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the Food and Drug Administration (FDA) has launched several initiatives and procedures to shorten the time from submission to drug commercialisation. For example, the Pandemic and All-Hazards Preparedness Reauthorisation Act of 2013 defined the framework for the use of a drug prior to licensing under specific conditions, and the FDA instituted the Emergency Use Authorization (EUA) procedure. The EUA procedure was used extensively in late 2020 and 2021 to authorise the use of COVID-19 vaccines and treatments even before their formal approval by the FDA. The European Medicines Agency and other HAs also started initiatives for acceleration of evaluation procedures in 2020 in response to the pandemic.

At a time when tens of thousands of people were hospitalised with COVID-19 and entire countries went into lockdowns, every day counted. The stakes could not be higher, and neither could the challenges.

Less haste, more speed!

Accelerated submissions may force teams to reduce document production timelines quite drastically, from 4 months to 4 weeks in cases of hyper-acceleration. Working longer hours is not sufficient to meet such aggressive timelines; after



all, pandemic or not, we still have only 24 hours in a day. Stress, fatigue, and sleep deprivation can lead to errors and result in poor document quality.

Increasing resource allocation to the submission is not sufficient either. Experience shows that resource requirements increase exponentially as timelines shorten. For a 4-week submission, the applicant may need 20 writers, or even more, depending on the complexity of the dossier. In a typical submission, the team writes the pivotal study CSR before the HLDs, as such a staggered process facilitates content reuse. In an accelerated submission, a staggered approach is not always possible, and several documents may be authored in parallel. Maintaining consistency between documents becomes a major challenge for the team. Coordination between writers working on different documents is an issue, and frequent team meetings reduce further the time available for authoring. Teams may find themselves in a situation where they can devote quality time to

their documents only over weekends.

To complicate matters, some events can force the applicant to conduct unforeseen post-hoc analyses or even change the regulatory strategy. Such events include unexpected clinical findings or feedback from HAs. In some cases, major comments from senior stakeholders can trigger a rewrite of some sections or entire documents.

Nevertheless, delivering a high-quality dossier is possible even under hyper-accelerated timelines. Preparation and process optimisation are essential for success, and medical writers should drive this.

Preparation and data-independent authoring

Teams should start preparing for a submission well in advance, several months before the database lock for pivotal studies. The first step is to set up a kick-off meeting where all submission-

related activities are discussed. The team must devise a clear plan for all these activities, including timelines for data-independent and data-dependent writing of clinical documents. Data-independent writing can start shortly after the meeting.

Teams should also consider preparing a storyboard, a concise, high-level distillation of all aspects of the clinical submission story. The storyboard is used to secure cross-functional alignment on key messages in the dossier and ensure stakeholder's endorsement of the submission strategy. The advantages of a well-developed storyboard are numerous, including an early focus on the desired label, clarity on the submission scope and purpose, and identification of any major scientific issues, gaps, and potential regulatory hurdles. Of course, the storyboard will have to be revised once the pivotal study data become available.

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During the preparation phase, teams may want to go a step further and populate data-dependent sections of clinical documents using shell or dummy tables. This approach helps to ensure that programmed tables and figures are adequate to support the key messages. In addition, it facilitates identification of gaps in statistical analyses.

When preparing for an accelerated submission, some teams want to write complete documents even before the data become available. Writing clinical documents based on dummy data can prove a risky venture, as it may give teams a false sense of security. When it comes to updating the documents using real data, simply replacing the dummy numbers with real ones often proves insufficient, especially in HLDs, which must present a critical analysis of the findings in addition to the factual summarisation of the data. Placeholder text must be rewritten with this imperative in mind.

Data interpretation

In the interest of time, some teams want to shorten data interpretation meetings or even skip them altogether and rely on medical writers to interpret the data. I do not recommend this approach as it is counterproductive. Even in the fastest submission, the team must find time to analyse the data and reach cross-functional alignment on the key messages. Early stakeholder buy-in is also important to reduce the risk of major comments during document review.

Data-dependent authoring, review, and QC

During the data-dependent authoring phase, medical writers should adhere to lean authoring principles and avoid repetition in HLDs. Instead of repeating information available elsewhere in the dossier, documents should provide links to the relevant CTD sections. Remember that any document available in the electronic CTD is just one click away. Ensure that the level of detail in each section is appropriate. CSRs tend to be more detailed, while HLDs should focus on the findings relevant to the benefit-risk assessment of the product and label claims.

Document review and quality control (QC) can be as challenging as authoring in a fast-paced submission. Reviewer discipline is always important, and it becomes critical when timelines are squeezed. Both the

number of reviews and their duration are reduced. I usually recommend 2 rounds of review for each document. A single review round may be sufficient if the number of reviewers is relatively small, between 10 and 20. In large companies, this number can go much higher, and the authoring team may receive hundreds of comments on a single document. In such cases, consider conducting a team review first, then a stakeholder/management review.

Reviewers should be encouraged to conduct strategic, substantive review. Medical writers have an important role in educating them in good review practice. Comments should be specific, directive, and based on facts rather than personal preferences.

Accelerated submissions do not always allow sufficient time for a separate QC step, therefore QC can be done in parallel with the last round of review. A final QC should be done once all comments are addressed, focusing only on changes made since the last draft. Medical writers should keep redline copies of documents so QC specialists can find those changes easily. Teams should avoid making any amendments to documents after the final QC, as last-minute changes can result in discrepancies and lead to other quality issues.

Teamwork, teamwork, teamwork!

Effective teamwork is essential in accelerated submissions. The whole submission team must work as a well-oiled machine, with efficient processes, well-defined roles and responsibilities, and clear communication lines. Any duplication of work should be avoided; content should be reused as much as possible, and teams should refrain from rewriting text that has been reviewed and approved.

Submission lead and team structure

Every team of medical writers needs a submission lead. In an accelerated submission, the lead does not always have time to author documents. The rule of thumb is that the team needs at least one person in charge of coordination for every 10 writers. For example, a team of 22 writers requires at least 2 full-time coordinators. Such a large team should consider preparing a charter to ensure everyone is aware of their roles and responsibilities. Also, it may be helpful to set up sub-teams to facilitate coordination and communication, with sub-team leads reporting to the submission lead.

Regular meetings are a necessity; however, teams should find the right balance between attending meetings and working on documents. Submission leads and coordinators should attend all meetings relevant to the submission, while writers of individual documents should attend only the most important ones, for example data interpretation meetings.

Time zone differences

International teams can leverage difference in time zones. Such teams can work round the clock while maintaining a reasonable work-life balance for each of their members. This approach can prove particularly effective for global submissions with a large number of documents and challenging timelines. It works best when there is a coordinator in each time zone, for example one in Asia, one in Europe, and one in North America.

Ensuring consistency throughout the dossier

As already mentioned, maintaining consistency throughout the dossier is a major challenge in accelerated submissions. The submission lead has a key role in this endeavour, but in reality a single person does not always have time to review every document in detail. Writers should also review each other's documents to facilitate alignment. For example, the authors of efficacy, safety, and pharmacology summaries should review the corresponding sections of the CO. Ensuring consistency of safety messaging between CSRs, SCS, CO, and RMP is also critical.

Challenges are also opportunities

Delivering a submission dossier in record time often seems a daunting task; however, bear in mind that with great challenges come equally great opportunities. Successful accelerated submissions foster a spirit of cooperation and camaraderie that can last for years and benefit the team in many ways. They are also an opportunity to innovate and optimise company processes. Finally, they are an excellent opportunity for professional development for all members of a submission team.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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