

Post-approval regulatory writing – How different is it from writing pre-approval documents?

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Abstract

Regulatory writing has various facets to it with good writing skills as a preliminary requirement. Well written reports form the basis of all regulatory submissions for marketing approval and its success largely depends on the research information presented to the regulators. Submission package should comply with the required guidelines and report structure. In addition, they should be written in a style that allows regulators easy access to the safety and efficacy information needed for making a decision on marketing the drug. Post-approval writing can present some interesting situations and challenges to the sponsor and the medical writer. It is important for a medical writer to be aware of these situations and make the necessary plans to surpass them, working with experts in different domains to ensure timely availability of the right drug to the right patients. The article describes in detail some of these situations.

Keywords: Pre-approval writing, Post-approval writing, Submission package, Sponsor, Guidelines, Regulatory agency

Background

Pharmaceutical regulatory writing involves writing documents, which provide information on research and development (R&D) conducted by a sponsor company, that are required by regulatory authorities to grant marketing authorisation for an investigational drug. Pharmaceutical companies create an extensive plan for the development of a drug. A typical drug development approach is to identify a potential drug candidate that would provide benefit for a particular medical condition, driven by an unmet medical need in the population. After the drug passes through laboratory and animal testing, clinical studies are conducted to answer

important scientific questions – is the drug efficacious for the indication, and is it safe for use in the intended population?

The clinical development plan (CDP) document acts as a blueprint to help the sponsor plan and conduct R&D activities required for approval of the drug for a particular indication. The various clinical studies and analyses conducted as a part of R&D are parts of a complex jigsaw puzzle. The individual component becomes clearer when the development step is documented and a report is written. This role is usually accomplished by a regulatory medical writer working with others involved in R&D. Health authorities provide detailed guidelines on the templates and document structure in which information needs to be presented for the marketing application. For example, the European Union (EU), which is an ICH-compliant region, provides clear guidelines in its European Medicines Agency (EMA) website.¹ Regulatory medical writers are required to work in accordance with the regulations and guidelines provided.

Once substantial evidence for the safety and efficacy of the product is gathered from clinical and non-clinical studies, the product is eligible for an application towards its marketing approval for an unmet medical need. Drug development is not limited to all the activities conducted before a sponsor applies for approval of a drug for an indication; a large part of it continues after that. The sponsor develops the CDP to strategise and prioritise parts of R&D needed for the initial approval, while the other parts of R&D are planned later for the registration of other indications.

Summary of documents written by regulatory medical writers

The common technical document (CTD) is the prescribed format in which clinical submissions are

made in the regions falling under ICH and also some other countries. The guidelines specifying details of the components of CTD exist on the regulatory websites (such as EMA for the EU region).² If a sponsor submits a CTD file to the regulator, writing of all the reports contained in that CTD file is called pre-approval documentation/medical writing. Document writing after the initial submission, in response to the assessment by the regulator³ or as part of R&D for other indication(s), is called post-approval medical writing. Some examples of post-approval reports are:

- (a) Reports for studies requested by the health authority (typical Post-Authorisation Safety Studies (PASS)), and safety-related reports such as Periodic Safety Update Reports (PSUR) and Risk Management Plans (RMP).
- (b) Reports for studies conducted to extend the indication to other populations. For example, imagine that Drug X was initially approved for all adult patients with essential hypertension without any comorbid conditions. Other related populations in which the drug efficacy might be tried are – the paediatric population, hypertension due to secondary causes, hypertension in pregnancy, geriatric population, or patients with comorbid conditions (diabetes mellitus, heart failure, etc.).

Regulatory writing should be clear, evidence-based, well-organised, and complete taking into consideration the regulators who are the end users. Although regulatory writing needs to meet a lot of criteria to be seen as a neutral account of what was done and what the results say from the studies and analyses conducted, it would be fair to say that the 'art' of good writing enables presentation of the right information to the regulators such that they are not lost in a sea of information and have the right information needed for them to make the decision as to whether the drug works or not. Also, the structure of writing the reports should help them gather information for the questions they might have on the reports submitted to support them in making decisions on marketing the drug. Faster drug approval fulfils the unmet medical need and leads to its quicker availability to the needy patients.

Some examples of documents covered under regulatory writing are described in Table 1.

Sponsors typically approach regulatory writing by having writers within their organisations and also by utilising external support of writers with

Table 1: Examples of regulatory documents

| Document category | Description |
|----------------------------------|--|
| Clinical study report (CSR) | Guided by the ICH E3 guidelines, ⁴ it is a report of an individual clinical study integrating various components of the study conduct, results, and interpretation |
| Summary documents | These are documents that summarise the results from various parts of R&D, focusing on key areas like efficacy and safety. They form Module 2 of the CTD ³ |
| Investigators brochure | A compilation of clinical and non-clinical data that facilitates the investigator to conduct the clinical study ⁵ |
| Safety reports | Development Safety Update Reports (DSUR), Periodic Safety Update Reports (PSUR), and Risk Management Plans (RMP) are some of the safety reports prepared by sponsors as a regulatory requirement during development or marketing of the drug in the EU region ⁶ |
| Health authority questions (HAQ) | These are post-submission assessment reports from the regulators ³ requiring the sponsor to clarify the issues raised and hold a key role in approval of the drug by the regulatory authorities |
| Briefing book | These are documents created by the sponsor to engage in active dialogue with the regulator, cutting across the various modules of CTD to bring together all the key information required by the regulator for their assessment |

specialty in a particular type of regulatory writing. Usually the writers working in the organisation are well aware of the sponsor drug development strategy and are able to assign the priority and focus required for some of the regulatory documents. External writers, however, bring their expertise in a particular therapeutic area or a regulatory document. The sponsor is required to plan effectively on which writing task goes to whom and there is no 'right' approach.

Preapproval regulatory writing

The focus of regulatory writing prior to marketing approval is to ensure the results of drug R&D activities are presented in the correct format within the template guidance provided by ICH. It accounts for answering the questions that were the objectives of the studies conducted and builds comprehensively on the information that has become available from all the research done on the molecule. It has to be comprehensive to ensure that all the relevant information generated, reaches the regulators in the most organised fashion. It should deter regulators from rejecting the application merely due to missing key information. Health Authorities usually come back with questions that need to be

addressed appropriately using tactful writing skills. The end result of a poorly written marketing application for a genuinely beneficial drug is delayed drug availability to the patients.

The skill sets required to write the different documents can vary substantially.

- Writing a Clinical Study Report needs a good understanding of research methodology and basic statistics to interpret the results and give a clear account of study conduct, results and the conclusions drawn from them.
- Writing summary documents and briefing books for the regulatory authorities require a far more impactful approach. The writer should have a good understanding of the drug development process. The writer should know how reports from various departments impact the decision by regulators for marketing the drug. The art of simplifying and presenting the key information is hard to master; however, that is exactly what the writer has to do – take the huge amount of information generated over years of research on the molecule, and present it in a way that helps the regulators make their decision. A lot of effort goes into data mining for the right information. Also, knowledge over various domains is required, such as regulatory requirements of the region where the submission is planned, what the regulators expect from the submission, and whether all the key questions with regard to safety and efficacy of the product are addressed adequately. Incomplete information can result in rejection of an application or further questions from health authorities for clarity. Some of these questions might require further studies to be conducted, thus pushing back the target approval of the drug by years.

Post-approval regulatory writing

Post-approval writing for any research is conducted, as described above, to augment the approval provided by the health authority or to apply for marketing of the drug in a new indication based on additional R&D. If the writing is for studies mandated by the health authority as a condition to give approval, it has to reach the regulators within the stipulated time to avoid delay in the planned marketing of the drug to patients.

If a writer is involved with writing a report for a study that was conducted for an indication other than the one the drug is approved for, the writer

has to think carefully about the following points while drafting the report:

- (a) All the relevant efficacy and safety data is presented well, without allowing a chance for interpretation that some of the information is missing in the documentation. This can impact the marketing status of the drug for the primary indication.
- (b) The report writer should evaluate (along with the other authors of the report) how the information generated from the study fits with the information covered in the preliminary submission that is available with the regulators. Also, whether the information is contradicting with, or is in line with the results achieved from pre-approval studies, needs evaluation. This is extremely challenging because the report should always be written to avoid any scope of misinterpretation, even if the new information generated puts the marketing status of the drug for the primary indication at stake.

A lot of interesting and unique situations arise in post-approval writing. This is because the sponsor wants to ensure that they are able to identify other unmet medical needs which can be fulfilled by the drug which has received an initial approval. The sponsor might approach filing for approval for the claims for benefits in another indication immediately following initial approval or it might require a longer duration of R&D and experience from marketing of the drug before being able to file for additional claims.

Some interesting facets of post-approval writing are described below.

Engaging writers for post-approval writing

Once a submission is done, the team including the writer(s) involved in submission activities usually get reassigned to other tasks. For post-approval writing, should the sponsor engage the same writer(s)? Reassignments are part of business today as sponsors try their best to manage the resources and manage the risk associated with some of these reassignments.

A new writer like any other new team member would need time to start contributing effectively. This means that it would take time for the writer to do their homework on the reports written in the past and the influence they have on the writing task at hand.

A writer who was involved right from the start can help bring perspectives from previous documents and ensure that the post-approval documents

are in sync with the previous documents submitted. A new writer brings in a new perspective, experience, and strategies from other submission documents they have written in the past. The sponsor has to decide on resource optimisation and priority of the project, which determines who ends up writing the regulatory documents.

Duration between initial approval and post-approval writing

Writing regulatory documents in continuity after the initial submission, works well for the sponsor as long as other claims from the drug are planned. However, there could be situations when new studies are conducted a long time after the initial submission with the drug already in the market. In this case, it is not always possible to have the same team that worked on the initial submission to be part of the new R&D and writing requirements. Challenges faced by this team would be to ensure that the data on the initial R&D is supplemented with the marketing experience, and the safety and efficacy data is based on its use in the population.

Safety reports post-approval

Safety takes a special focus when the drug is marketed in the population. While R&D is conducted prior to submission, only a small portion of the population who were enrolled in the studies is exposed to the new drug. With marketing approval, larger populations get exposed to use of the drug and adverse effects not evident from the early clinical trials may become more apparent. From the regulatory writing point, writing periodic reports such as Periodic Safety Update Reports (PSUR) presents to the regulators the safety profile of the drug and reasons why the drug should be marketed further. The RMP document is written to ensure that the adverse events related to the medication are well managed by various modes such as label information, education of patients, use of social media, etc. As long as clinical drug development is continuing post-approval, a Development Safety Update Report (DSUR) is mandated, with the focus to communicate to the authorities what is the drug benefit–risk profile for continuing drug development.

Writing follow-up reports for reports in the submission package

There can be further challenging situations while writing documents post-approval. Imagine a case where results of an interim analysis of a study were submitted to substantiate the claim of the drug for approval. When the whole study gets completed, well after the approval for the drug, the

writer might find a situation where the results can vary from the interpretation made at the interim analysis. This could be because the data generated from the site was ongoing and follow-up information might impact the interpretation made for interim analysis. In this case, what should be the approach? We are bound by ethical standards to ensure that the health authorities are aware of this situation and only drugs with the right benefit–risk ratio reach the patients. But imagine the pressure the writer has to face to ensure that the results are presented in a fashion such that there is no room for misinterpretation!

Conclusion

Regulatory writing is an extremely specialised job that is done by individuals with a capability of depicting information in both, concise and precise format. It requires a lot of cross-functional interaction, planning and influencing to ensure the right message is presented in the reports. Writing documents pre- and post-approval has its own set of challenges. The examples illustrated above point towards the expertise needed and the strategic approaches required to plan and execute regulatory writing pre- and post-approval. From a writer's standpoint, it is important to understand drug development and the challenges that come up as a part of the process, and the constant push to get the right drug to the right patients. A lot of thought process goes into writing regulatory documents and the role of the medical writer is key to substantiate that the right drug should reach the right patient population and the regulators are convinced to make this decision.

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Author information

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Errors and corrections

We all make mistakes, right? I once spotted an error in the title of a scientific paper some colleagues had got published. Instead of *Familial* they had written *Familiar*, the reason being that the Swedish word *familjär* can have both meanings and they picked the wrong one. Quite how this got past the editor and reviewers I do not know. But anyway, the authors published an erratum and got the title corrected.

While unfortunate, this mistake was relatively trivial. It did not lead to data being misinterpreted or erroneous conclusions being propagated. Noting that ‘Errors serious enough to invalidate a paper’s findings may require retraction’, the International Committee of Medical Journal Editors (ICMJE) includes guidelines on errata in its Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.¹

To assess, among other things, whether the ICMJE guidelines are being applied, a group of researchers from St. Louis searched for and analysed errata published in 20 leading journals (10 in general medicine and 10 in cardiology) over an 18-month period.² They found 557 published errata, nearly 40% of which appeared in the *New England Journal of Medicine* or *The Lancet*. Erratum rate was positively correlated with journal impact factor. Alarmingly, only half of the errors classified as ‘major’ had been corrected.² This in spite of the fact that 540 (94%) of the articles requiring errata were published by

signatories to the ICJME guidelines, according to which ‘The journal should post the new article version with details of the changes from the original version and the date(s) on which the changes were made’.¹

The St. Louis team call for a ‘consensus about errata reporting’.² Well, what are the ICMJE guidelines if not some kind of consensus? Rather than lack of a consensus, the problem seems to be the inevitable failure of authors, reviewers, and editors to spot every error, and the non-inevitable failure of journals to adhere to existing guidelines concerning corrections.

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