

Help Reviewers Tell You What They Want

Reviewers of regulatory documents need to ensure that their comments are specific, actionable, and relevant, so that no critical time is spent unnecessarily throughout the document development process

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Review is an integral part of the medical writing process and relies on clear communication between the medical writer and the reviewer(s). This is a two-way street. Review can be a frustrating process for both the writer and the reviewer(s) when there is miscommunication.

Thus, both parties are responsible for ensuring that the review process runs as smoothly and efficiently as possible. Ultimately, there is no ‘us’ and ‘them’ in the document development process, but a common goal to be reached within a clearly defined timeframe by a team: finalising fit-for-purpose documents for submission to health authorities, which will ideally result in a successful marketing authorisation approval.

My aim in this article is to give us medical writers hands-on tools for improving the communication with our reviewers by making our review expectations more clear. I am presenting specific, simple principles that reviewers can practise throughout the document review process until they become habitual, including examples of how to provide comments that are unambiguous, actionable, and relevant.

What Review Is and Isn't (Or at Least Shouldn't Be)

Review is a process conducted at different stages of document

development to ensure that a document meets its purpose, i.e., that it is complete, coherent, and aligned both with the overall strategy of a specific project and the expectations of the intended ultimate audience, which, for regulatory documents, is always the health authority (not the manager of a certain reviewer!).

Review differs from quality control (QC) in many aspects. Review should not be a check of numbers, spelling, and company-specific style guide conventions. Ensuring that these aspects are met falls under the responsibility of the medical writer throughout all document development stages, and of QC specialists and document managers/administrators at later stages; such responsibilities are usually defined by a company's standard operating procedures (SOPs).

While it is often easier for reviewers to check abbreviation lists, fix spelling errors, and propose taste-driven linguistic changes on already linguistically correct text (1), what we ultimately want as medical writers from our reviewers is something else: constructive, unambiguous, and timely strategic input ('strategic review'), primarily on document sections relevant for each reviewer's functional role ('function-driven review') and on each document, considering both the document type ('eCTD placement-driven review', based

on its place/purpose within the electronic common technical document [eCTD]) and the document development stage ('staged review').

Reviews Are Sometimes Poor, but We Can Change This

Several studies have shown that inefficient reviews are not uncommon across the pharmaceutical industry. Throughout several review rounds, the reviewers were asked to categorise their own comments on a specific document into one of the following categories: rhetorical (content-related/strategic), editorial, and stylistic; they assessed their comments as largely rhetorical. When the consultants looked at the drafts and categorised comments based on more objective criteria than personal opinion, they found that the vast majority were in fact editorial and stylistic, even on advanced drafts of the document (2-3). The question is: why? Various reasons account for the often ineffective and inefficient review process seen across the industry, most of which are largely unintentional and can be at least partially corrected with appropriate training.

We should not forget that reviewers aren't primarily reviewers; they have been trained to be experts in their field (e.g., statistics, bioanalytics, or clinical research), not communicators. While exercising their role in a pharma company, they wear many hats, and the



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‘reviewer’ hat is just one of them. Often, they could even be quite frustrated that the medical writer and other reviewers do not understand what they want. After all, their comment was quite clear!

Some reviewers do not have a clear understanding of how their review needs to change based on document type or document development stage, especially in companies that do not provide sufficient training on the eCTD structure during the initial onboarding phase. A reviewer will often approach a document with the same ‘strategy’, regardless of whether this document is, e.g., a clinical study report (CSR), a clinical summary of safety (SCS), or a clinical overview (CO), reading it page by page, largely focusing on things like abbreviations and spelling, and gradually reducing the number of his/her comments by the time he/she gets to the results and conclusions sections.

In short, the expectations and objectives of the review are more often than not unclear for reviewers, although medical

writers may think otherwise. It is up to us medical writers to recognise such issues and train our reviewers without sounding patronising. In 2015, Douglas Fiebig laid down the ‘six vital ingredients’ for how to ensure a great review process across multiple cycles (1):

- Define a structured review process
- Use a collaborative review tool, i.e., PleaseReview
- Clarify review expectations
- Implement staged reviews
- Plan review as a defined activity
- Enforce the review process

I have worked in different pharma companies and also on the vendor side. Therefore, I’m very aware that the medical writer’s role is defined differently in different institutions, and I’d advise you to always raise awareness about the role played by medical writers in developing documents and in the industry in general, and, to clarify, the responsibilities of all parties

involved, even if these are already covered by an SOP.

For us medical writers, it may be obvious that in addition to writing, we do not only manage timelines, but also act as mediators in case of conflicting strategic comments, bringing discussions back on track during meetings and making sure that timelines are kept. In line with this, we do not bring all comments provided on a draft to a comments resolution meeting (CRM), but only critical and at times conflicting comments from different reviewers. Keep in mind that some reviewers may have either worked with medical writers in a different setup in another company (and, therefore, have very different expectations from us than we assume) or may have never even heard the wording ‘medical writer’ before, especially if they are new to their role in the pharma industry.

If a reviewer is, e.g., working on a submission for the first time (even if he/she does not wish to openly acknowledge this), an experienced medical writer can also be a resource for regulatory guidance, eCTD structure basics, and roles of different team members during document development, beyond what is already covered in sometimes multiple and lengthy SOPs. A kick-off meeting for every writing project is a good starting point to set such things straight.

The following aspects and tools that I provide, (and, in particular, the tabular presentations) could be introduced at



When we mentor and review junior medical writers’ documents, we should, of course, also adhere to the same principles



| Before review | |
|--|--|
| 1 | Get familiar with the eCTD structure, SOPs, and relevant regulatory guidelines. Put yourself in the shoes of the ultimate target audience (health authority for regulatory documents). They need to make a yes/no decision, rather than be educated. With this in mind: what do they require to know? |
| 2 | Get familiar with the source data (CSP, SAP, CRF, TFLs, etc.) and do not ask for changes that can no longer be implemented after DBL (e.g., in primary analysis, additional sensitivity analysis after second draft CSR review, etc., close to submission deadline, adding data not in the database, etc.) |
| 3 | Get familiar with the electronic review tool(s) used (document management system, e.g., Documentum or collaborative review tool such as PleaseReview) and use its capabilities |
| 4 | Once you have agreed on timelines, make yourself available. Plan time ahead (in your Outlook calendar; ask your personal assistant [PA] for support). Delegate your review if you know you will be away on vacation and guide your back-up through the basics of the project and review expectations before your vacation. Inform the medical writer of your absence and contact details of your representative |
| During review | |
| 5 | Focus on: <ul style="list-style-type: none"> • Providing input on relevant sections for your functional role/area of expertise, keeping in mind the document type (based on its place in the eCTD structure) and document development stage • Providing strategic input on content in the form of specific, actionable, and relevant comments* • Categorising your comments into: major-critical, minor-not critical, cosmetic, and avoid wordsmithing based on personal taste and checking abbreviations or numbers in programmed in-text tables |
| During the CRM | |
| 6 | <ul style="list-style-type: none"> • Come prepared to the CRM • Consider other reviewer's comments • Propose pragmatic solutions (ensure a balance between the required content and the target submission date), especially for critical comments that may require a change in strategy or additional analysis; consider whether this comment is truly critical at this particular stage |
| After the CRM | |
| 7 | Offer support to the medical writer in addressing any still open challenging comments if needed |
| CRF = case report form, CRM = comments resolution meeting, CSP = clinical study protocol, SAP = statistical analysis plan, DBL = database lock, and TFLs = tables, figures, and listings | |
| * The review cycle continues and steps 1-7 are repeated for the next stages, until document finalisation | |

Table 1: The responsible reviewer's checklist

the kick-off meeting with each clinical team you work with, but it is also a good idea to incorporate them in routine cross-functional trainings, to be held both during the onboarding phase and as refresher trainings, at least once a year within a given organisation. In addition, laminated hand-outs with key principles and specific examples are always useful at the end of such trainings. The reviewers can keep them

on their desk and use them on a daily basis while conducting reviews.

Last but not least, when we mentor and review junior medical writers' documents, we should, of course, also adhere to the same principles. It is up to each and all of us medical writers to create, enforce, and maintain good writing and review practices across the industry.

The Responsible Reviewer's Checklist

Consider introducing reviewers within your organisation or at the client's site to a tool that I like to call "the responsible reviewer's checklist" (see **Table 1**). In addition to including it in trainings, I'd also suggest attaching it as a pdf when initiating review cycles and whenever you send a document for review to senior management, either directly or through

someone else (e.g., medical/clinical expert, regulatory affairs manager, or the senior manager's PA). Senior managers are unlikely to attend your trainings, but will at least be informed of your expectations, and you might end up being positively surprised with the results of this exercise. Also, talk to their PA well in advance to set aside time for document review in their calendar. Overall, this tool can be an effective way to create a common understanding within a document development team of what the review process entails.

Focus, Focus, Focus!

The need for a focused review may seem obvious, but I have nonetheless very often seen statisticians 'improving' document wording based on personal taste (and thereby at times changing the meaning of a sentence that was once correct), clinical experts checking the list of abbreviations rather than focusing on the clinical interpretation of data, regulatory affairs managers adding two spaces instead of one after each full stop throughout an entire document (while ignoring company-specific style conventions), and the list could go on. I am sure that all of us have had such experiences with different teams and we can all agree that this is not the kind of feedback we wish to receive throughout the review cycles of a document with tight timelines to be met and critical data to be interpreted. It is both ineffective and inefficient.

My experience is that teams need to be reminded of what to focus on, based on their function, document type, and document development stage. Last but not least, some reviewers tend to lose track of the ultimate audience of regulatory documents (the health authority!), and instead anxiously focus on how their line manager will perceive their review. As medical writers, it is part of our job to bring reviewers back on track and remind them of what to focus on (see **Tables 2-4**).

Somewhere around the time of the final draft (e.g., after second draft review), the QC step will take place.

| Role | Focus |
|----------------------------|---|
| Clinical expert | Medical background/unmet medical need |
| | Clinical interpretation and relevance of results |
| | Overall consistency of messaging across sections and clinical programme |
| | Benefit-risk assessment |
| Statistician | Description of statistical methods and statistical interpretation of endpoints |
| Regulatory affairs manager | Adherence to regulatory guidelines specific for the respective class of drug and therapeutic area, and addressing regulatory feedback received throughout the clinical development programme (on study design, safety, etc.), if applicable |
| Clinical pharmacologist | Pharmacology methods and results |
| Clinical study manager | Description of study conduct |
| Bioanalytical expert | Description of bioanalytical methods |
| Senior management | Alignment of key messaging with overall product and company strategy |

Table 2: Focus of review by functional role/area of expertise (function-driven review)

| Document type | Purpose within eCTD | Focus |
|--|--|---|
| CSR (4-5) | Reports methods applied in an individual clinical study and clinical study results (4-5) | How the study was conducted and how results are reported at individual study level; most detailed clinical data presentation |
| SCS/module 2.7.4 | Summarises safety data relevant for a particular regulatory submission (6) | How safety is summarised across studies (usually in safety poolings); intermediate level of detail |
| CO/module 2.5 | Is a critical appraisal of the data in a clinical submission; it provides the clinical context of the data and a benefit-risk assessment that should ultimately support the proposed label (6) | How results are critically evaluated in support of the proposed label; benefit-risk assessment is essential and should be supported by the rest of the document and aligned with the SmPC, USPI, and RMP; data are not presented again at the same level of detail as in individual CSRs and summary documents, but critically assessed |
| RMP = risk-management plan, SmPC = summary of product characteristics, and USPI = US prescribing information | | |
| * In the world of electronic submissions (as most submissions tend to be nowadays), reference documents are just one click away in the electronic common technical document (eCTD) structure | | |

Table 3: Focus of review by document type (eCTD placement-driven review)

| Document development stage | Focus |
|----------------------------|---|
| Shell | The methodology is complete and accurately described The data presentation strategy is defined and fit for the purpose of this specific document (considering the class of drug, therapeutic area, and eCTD location) The use of tables vs text is agreed within the team and adequate The inclusion of endpoints is accurate and complete Key conclusions/study objective will be supported by data shells |
| First draft | The interpretation of the data is correct The document is complete (everything needed is in, and nothing is missing) |
| Second draft | First draft comments have been appropriately addressed Key messages are clear and consistent within the document and across the entire project (not only on the clinical level, but also consistent with pre-clinical data) |
| Final draft | High-level messaging adequately supports overall project filing strategy |
| Final version | The document is fit-for-purpose |

Table 4: Focus of review by document development stage (staged review)

Inform your reviewers, as applicable at each draft stage, that the document has/has not yet been QC-ed. The second or final draft is usually also reviewed by senior management and/or the principal/coordinating investigator. Other reviewers, such as key opinion leaders, may also be involved at this stage. Reviewers belonging to the core clinical team need to be ready to tackle any challenging, strategic, conflicting comments coming from these additional reviewers at CRMs. Medical writers should remind core team members of that, and potentially also ask them to align with their functional line managers early on to avoid very late surprises (to the extent realistically possible).

Train Reviewers on How to Make Their Comments More Specific

Providing good comments takes substantial time during review, but will avoid a lot of confusion within the team later. Learning how to provide good comments also takes time, but once this has been learnt and applied, it pays off for everyone involved in the development of a document. The reviewer is required to take one step forward and not only identify a problem (by simply criticising: 'this is bad'), but also provide a solution.

This requires both some thinking and often even digging into the data; however, this is the only way in which a review is actually 'complete', although a reviewer emailing you saying "I have completed my review" may have thought otherwise. Without a proper and truly complete review, the review process does not add much value; it uses time and resources, and makes us medical writers feel like we are pulling teeth at CRMs.

Replacing broad questions with specific answers and clear rewording suggestions pays off, but we need to train our reviewers and put them in the shoes of those receiving poor comments, clearly showing them why their comments aren't as clear as they may think (see **Table 5**). As medical writers, it is up to us to give reviewers the opportunity to see how it feels to be at the receiving end

of poor comments, and make them think and practise (after providing them with guiding principles) how to better word comments. As a rule of thumb, comments should be:

- Specific and constructive: "this is bad" written on the front page of a document does not indicate what is bad and does not help the team move forward and improve the document – pointing out specifics of what is bad and suggestions on how to 'correct' the bad part does
- Actionable: using an action verb ("add/write/refer to x, y, z"), not an open question ("What about adverse events?" or "Why didn't you describe adverse events?"), to which the writer may think "Aha, yes, what about them?" or "Because I didn't want to") is always better
- Relevant: reviewers should consider the timing and relevance of their comment before asking for a major change that would either completely change the structure or is too late (keeping the target submission timeline in mind) to address (e.g., we cannot redefine the primary analysis of a study post-hoc [after database lock]). There is a difference between a 'nice to have' comment and a 'critical' one (a must for the team to consider and discuss)

It is essential that we are clear about what we want and how we want it done. We medical writers should clarify what we want the reviewers to focus on and how comments should be provided, ideally well ahead of the start of the review process, i.e., at the kick-off meeting. If reviewers understand what is being asked of them, those of us wearing the medical writing hats will hopefully receive comments that are easy



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| Usual comment | Why the comment is not helpful and how to improve it | Better comment |
|---|---|--|
| “Can we align this with our recent project X?” | The writer may not have worked on this older submission. Moreover, is the request to specifically align a sentence, a paragraph, using a similar table? The writer may not know what is being asked. If it is just one sentence that you want used as a prototype, look it up yourself and provide it directly during review | “Please describe serious infection results as follows: ‘Patients treated with drug X are not at a higher risk of developing serious infections than patients treated with drug Y’” |
| “This is bad” (1) | What is bad? The writer cannot know what is bad (a word, a sentence, a paragraph, the whole document) and how to improve it; provide an alternative | “Please reword this sentence to x and y because...” Include a reason for your request |
| “What about allergic reactions?” | It is not specific and not actionable. The level of intended detail is not specified. There are different ways of presenting such results. For the writer to address this comment, a discussion is required. Check the data yourself and consider their key message, then propose a specific data presentation strategy and wording | “Please present allergic reactions in tabular format by treatment group” or “Please add ‘Allergic reactions were reported in 1-2% of the patients in each treatment groups’ (I have already checked the data myself)” |
| “Refer to Figure 8 and place in context” | The writer can easily add a reference, but “place in context” does not provide the content that the reviewer would like to see added. Clarifying the regulatory or clinical context in specific wording would help in this case | “Please add: ‘...as described in Figure 8. This result is particularly relevant for patients with advanced disease X who do not respond to standard first line therapy with drug Y’” |
| “Should we use the word inhibitor or antagonist?” | It is a question; quite likely, it has been asked before within the same team, for the same document, and the discussion is becoming redundant – make a proposal | “Please use ‘antagonist’ throughout the document and use it consistently across this clinical programme” |
| “Can we add more information on cardiovascular events?” | Usually the answer would be: “Yes, we can (if we have the data),” but what to add? Only serious events? Only fatal ones? A table? Only text? Information on those leading to discontinuation? This kind of comment shows that the reviewer did not make the effort to look at the data and think of what needs to be added with priority – make comment more accurate | “Please add frequencies of patients reported with serious cardiac events by treatment groups, then add ‘No clinically relevant differences were seen among groups’ (I have already checked this; reference: Table 15.3.4.5)” |
| “Why aren’t you presenting haematocrit values?” | “I didn’t want to” could be the answer. The comment does not specify if values should be presented as table or text, i.e., the key message of these data is missing. It is also not clear why singling out this lab parameter is considered relevant. Leave no doubt about what you want and propose specific wording to be added | “There’s a concern of a drop in haematocrit values with this type of drug. Thus, please add ‘Unlike with other inhibitors of class X, no decreases from mean baseline values were seen in this study (Table 15.3.10.2)’” |

Table 5: Why some comments are ineffective and how to provide better comments



to implement and do not require endless discussion at CRMs.

Conclusions

Nobody is born a reviewer. Review is a skill that can be taught and learnt. As professional medical writers and communication experts, we should take the time to train our teams both on our and on their responsibilities when it comes to document development, not all of which can be covered by an SOP. In particular, we should train them on how to provide clear, specific, constructive, actionable, and relevant comments, thereby helping each team member meet his/her full 'reviewer potential'. Everyone involved in the development of a document will benefit from this, which will not only ensure a smooth collaboration, but ultimately will save the pharma company as a whole both time and money. Having the reviewers adhere to basic, clearly laid out principles when they conduct their review, aligned with their functional role, document type, and review stage, should improve the efficiency and effectiveness of the review

process throughout clinical development and across organisations.

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