Regulatory Matters

SECTION EDITOR

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Supporting post-submission interactions with health authorities

Medical writers are often involved in the preparation of submission documents such as clinical overviews and clinical summaries. The submission of the application (or, in the case of drugs already approved, a variation or supplement) is an important company milestone, but there is still plenty of work to do. After validation of the submission, the agency reviews the documentation, and a process of back-and-forth begins in which positions are negotiated and concessions may be made.

The details of this post-submission interaction vary according to the type of application and the agency. The European Medicines Agency has well-defined timelines, including so-called clock stops. This agency also usually provides all its questions at the end of the review procedure as part of an assessment report. In contrast, the US Food and Drug Administration is less bound by a pre-specified schedule and may also ask questions during the review procedure. But regardless of the details, the general approach is the same: a list of questions (sometimes called a Request for Supplementary Information) is issued, and the company prepares its responses. Questions can concern any aspect of the submission and may range from fairly simple ones, for example a request to provide a certificate of analysis, to complex ones, such as a fundamental challenge of some aspect of the interpretation of the results. Once the responses have been prepared, they are submitted to the agency for review. More than one round of questions may be needed to reach the end of this process, at which point the agency either approves the application, usually with certain conditions, or rejects it (or the company withdraws its application). For our colleagues more familiar with medical communications and submission of articles, this process can be considered as analogous to peer-review, in which responses to the comments from the peer reviewers are prepared.

Support from medical writers

The response-to-questions document is a central part of the post-submission interaction with the health authorities. For trivial questions (for example, the request to provide a certificate of analysis), little medical writing support may be required. For more complex issues, though, the medical writer may be able to offer valuable assistance for a number of reasons. First, the medical writer will likely have been closely involved in the preparation of the initial submission and so be familiar with the details of the project. If the list of questions is extensive, skills and know-how of medical writers, such as the ability to manage and oversee complex projects, coordinate input from a variety of sources, and ensure consistency, can be valuable to ensure high-quality responses. The process often requires working to tight deadlines, something that medical writers will be used to. Finally, the tone of the responses also needs careful consideration. The company should sound confident and sure of its position without being dismissive of the reviewers´ comments and questions. The language expertise of medical writers can also therefore be important.

Practicalities of response preparation

Before the Request for Supplementary Information arrives, it may be helpful to put together a response team whose members are able to dedicate sufficient time to the responses. The company may also have already made a critical assessment of the application, identified weak areas where questions are likely to be asked, and decided on a high-level strategy for response should these issues be raised during review. Preliminary assessment reports may also be sent to the company, and these can provide some indication of the thinking of the agency reviewers.

Once the actual final Request for Supplementary Information is available, the overall strategy should be finalised as soon as possible. The questions are not always clear and unambiguous and should always be interpreted in the context of the full assessment report, which may provide further clues about the concerns of the reviewers in case of doubt.

When the list of questions is extensive and the timelines are short, it may be helpful to classify the questions according to their level of complexity. Drafting of the response to the "easy" questions can begin straight away in a staggered approach to avoid a log-jam at the end of the process. It is also important to identify questions that may require additional statistical outputs to be produced as this may well be a rate-limiting step.

Final thoughts…

Preparation of responses to Requests for Supplementary Information can be stressful, but it is also rewarding. Preparation of the initial submission is only the start, and the medical writer will likely have worked hard within a team. Involvement in the post-submission process can give the writer the satisfaction of seeing the job through. It can also serve as feedback on how the original submission documents were prepared and provide some enlightenment on what goes through a reviewers mind. All this will deepen the medical writer´s knowledge of the approval process and help make him or her a more complete writer.