The FDA, EMA, and PMDA Questions: How to Respond During Review of CTD Submission Dossiers

After submission of the application dossier, it is essential that the team that prepared the application does not dissipate. Instead, it should prepare for the sprint that begins after the questions from the regulators arrive

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While the ICH's Common Technical Document (CTD) is an internationally agreed format for preparing application dossiers needed for obtaining approval to market a drug, the ensuing review process is specific to the country or region in question. Irrespective of the differences in process between countries and regions, questions will almost always be issued during the review process, with a request for written responses. These responses can be decisive for the outcome of the dossier review, and medical writers can make a substantial contribution to ensuring that appropriate responses are prepared within stipulated timelines. The types of questions posed can, in theory, be similar across countries and regions, and the main differences in the process lie with when the questions are received and the time available to respond. The challenge is, therefore, not only to prepare appropriate responses, but also to address the logistical challenge of submitting the responses on time.

Regional Differences in Issuing Questions Requiring Written Responses

A comparison of the standard review process in the US, the EU, and Japan illustrates strong contrasts in the review process for application dossiers and how and when questions are issued by the regulators (see **Figure 1**).

In the US, the applicant can expect to receive questions from the FDA at any time after the New Drug Application (NDA) is submitted until the action letter is received 10 months after submission, communicating the agency's decision (1). The questions may be sent individually or in batches, and there may be times during the review period when multiple batches of questions are received in short succession. In all cases the agency will specify a timeline for responding, which may vary from a day or two for simple questions to weeks for complex analyses and interpretation of the data.

In the EU, the review follows a set timetable (2). On day 80 (relative to the Marketing Authorization Application [MAA] submission date), the applicant receives the initial assessment report, followed by the formal list of questions issued on day 120 (the 'clock stop'), for which responses are required. The recommended time for responding to these questions is three months, with the day of submission being day 121 (the 'clock restart'). On day 150, the applicant receives the response assessment report, followed on day 180 by the formal list of outstanding issues (for which again responses are required). The recommended time for responding to these questions is one month, with the day of submission being day 181. No further questions requiring written responses are then

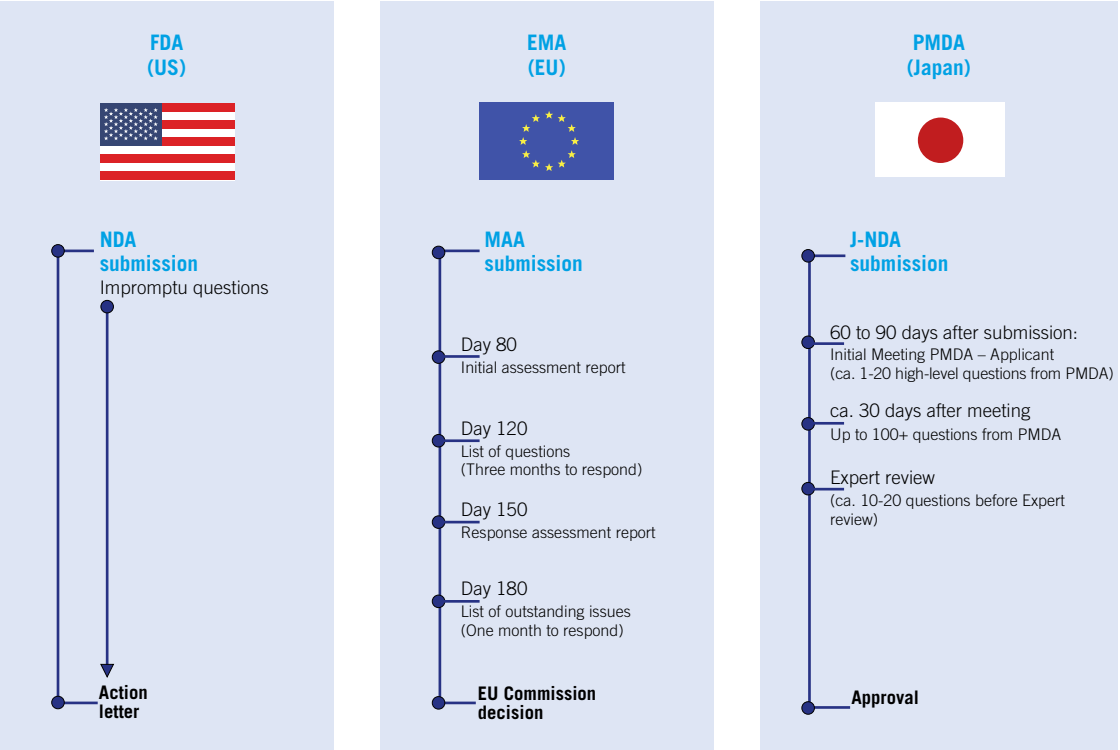

Figure 1: Simplified comparison of the timing of questions issued during review of CTD submission dossiers in the US, EU, and Japan

received before the formal opinion and accompanying assessment report are issued on day 210.

In Japan, the review process involves an initial in-person meeting between the Pharmaceuticals and Medical Devices Agency (PMDA) and the applicant approximately 60 to 90 days after submission of the J-NDA (3). At this stage, typically a small number of questions on high-level issues are provided by the PMDA to facilitate an exchange of opinions. At approximately 30 days after this meeting, the PMDA issues more than 100 questions requiring written responses within one month (4). While further meetings occur during the review period between the PMDA and external experts, also with a small number of questions on high-level issues provided by the PMDA to facilitate an exchange of opinions, typically written responses to questions issued by the PMDA are only required on the one occasion before the opinion on marketing approval is received at approximately 12 months after submission of the application dossier.

Logistical Challenges in Responding to Questions

The three regions summarised above all have in common that the volume and complexity of the regulatory questions issued are unknown to the applicant before receipt, but the different review processes result in different logistical challenges when responding to these questions (**Table 1**, page 50).

The US presents the greatest challenge on account of questions being possible at any time during the review period. The applicant must ensure that sufficient resources are available from all relevant functions over an extended period to ensure a response can be provided in the specified timeframe.

In the EU, the set timetable for receiving questions on days 120 and 180 enables the applicant to plan accordingly. Furthermore, the initial assessment report issued on day 80 provides reliable insight into the list of questions on day 120, and the response assessment report issued on day 150 provides reliable insight into the list of outstanding issues on day 180. In this way, the two occasions when written responses are required can be prepared for in a targeted manner, drawing on resources as needed rather than having to maintain the full spectrum of resources on standby for receipt of questions at any time.

In Japan, the high-level questions issued in association with the initial in-person meeting between the PMDA and the applicant provides limited insight into the more extensive questions received approximately 30 days after this meeting. The turnaround time of 30 days for responding to these questions is short. In practice, often the questions will be addressed by the applicant's team in Japan without involving a global team. However, if input to the written responses is required from a global project team, then this is typically required within approximately 14 days of the questions being received to enable the responses to be translated into Japanese before submission to the PMDA.

	FDA (US)	EMA (EU)	PMDA (Japan)
Timing of questions requiring written responses	Unpredictable, any time between submission of dossier and receipt of action letter	Predictable, on day 120 and day 180 after submission of dossier	Predictable, approximately 30 days after initial meeting between PMDA and applicant
Early insight into content and complexity of questions	No	Yes, on day 80 and day 150 after submission of dossier	Partial, from high-level questions provided for initial meeting
Early insight into number of questions	No	Yes, on day 80 and day 150 after submission of dossier	No
Timeline for providing written responses	Variable, specified on a question-by-question basis, days to weeks depending on question complexity	Three months for questions received on day 120 and one month for questions received on day 180	Typically, 30 days

Table 1: Comparison of process for responding to questions issued during review of CTD submission dossiers

Planning for Responding to Questions

After submission of the application dossier, which may conclude a lengthy and gruelling process, it is important to avoid having a project team dissipate and move on to different tasks. Almost all development programmes contain certain weaknesses or other issues of concern for regulators, generating questions during review of the dossier. The team that prepared the application dossier is best positioned to respond to such questions.

The reasons for questions being posed by reviewers may include information not being found or understood, and requests for further analyses. The questions can vary in nature from straightforward, technical questions requiring little or no medical writing support through to complex, scientific questions requiring extensive interaction between medical writers and the project team to draft and review responses. The questions may address any aspect of the submission.

Soon after the dossier has been submitted, irrespective of the region involved, a response team (preferably a rapid response team [RRT]) should be formed with representatives from all relevant functions for subject matter as well as from support functions, such as medical writing. As described above, depending on the region, the RRT may need to respond to formal questions on multiple occasions at any time during the review period (as with an FDA submission) or on predefined occasions (as with EMA and PMDA submissions). In any of these scenarios, it is essential that the team starts its scientific and logistical preparations before the questions arrive because once they do arrive then the sprint starts to prepare the responses.

Ideally, already during preparation of the dossier, the team should be documenting known scientific weaknesses or other issues in the dossier in anticipation of questions that may be asked. These issues may include weaknesses associated with the drug itself or its class of drug, deficiencies in the design or conduct of the development programme, deficiencies in data analyses, or issues of specific interest to regulators. Thought should be given to these issues starting soon after submission, when the pace is less hectic, on how best to respond. Ideally, potential questions should be answered before they are posed and any additional analyses that may be needed should be prepared pre-emptively. Time invested at this juncture can pay dividends when the formal questions are received and the RRT needs to respond in a short time frame. The challenge is to focus the project team on providing their input for addressing questions that have yet to be posed. Medical writers can facilitate the process by proposing structured and pragmatic means of capturing thoughts on topics, e.g., via text or bullet points in a spreadsheet, together with other practical information such as analyses still needed or the status or location of any additional analyses being prepared. In the case of EMA submissions, a benefit of the initial assessment report received on day 80 is that a focused approach to preparing responses for the consolidated list of questions received on day 120 can be made in advance of their receipt.

Logistically, before any questions arrive, the RRT must have a clearly defined and workable process for all the steps that need to occur between the receipt of questions and the submission of responses (see **Figure 2**). Tasks must be assigned, with a common understanding of task ownership and agreement on resource availability before the questions arrive. Provisional timelines can be drawn up for different classes of question

Figure 2: Process for preparing written responses to questions issued during review of CTD submission dossiers.
SME = subject matter expert; MW = medical writer

complexity. When the questions arrive, like the mechanics when a racing car enters a pit stop, the RRT must be able to react immediately to carry out their individual tasks without needing to expend time or energy on considering how or when they should be done, in what is akin to a well-rehearsed sprint. On receipt of questions by regulatory affairs, the initial project management tasks include tracking receipt of the questions, assessing the topic being addressed to identify the most appropriate subject matter expert(s) needed for preparing responses, and optimising the time available for preparing the responses. Depending on the region involved, the turnaround time may be specified by the agency on a question-by-question basis as questions are issued (as with the FDA), or else a longer time frame may be available for a batch of questions issued at a specific timepoint in the review process (as with the EMA and PMDA).

For any given subject area in the development programme, the drafting and reviewing team must be available and ready to devote their attention to the response workflow as soon as details of the question(s) are received. The timelines will need to take account of the time stipulated for submitting responses as well as the complexity of the questions, and may need to involve multiple rounds of (rapid) review before the content is final. If the responses need to be translated (e.g., when prepared by a global project team for the PMDA) and compilation of additional material such as statistical outputs and literature references is needed, then these steps also need to be factored in and will reduce the time available for drafting and reviewing the responses.

Writing the Responses

Typically, there is no regulatory guidance for the format and content of the written responses. Where possible, it is advisable to keep the format and layout of the responses consistent with the application dossier being reviewed. For each question received, it is essential to remain focused on the information being requested. All too often, subject matter experts can provide medical writers with more information than needed to respond to the question, or else they provide information that does not directly answer the question being asked. Medical writers should, therefore, ensure that the response team (authors and reviewers) remains aligned with the question being asked throughout the response process. New data cannot be submitted with the responses, but data already submitted in the application dossier may be reanalysed. As a general guide, reviewer friendliness can be ensured by making the responses as long as necessary and as short as possible. Reviewers are grateful for concise responses that provide them with the information being asked for, and nothing else.

> *The preparation of written responses to questions received during the review of application dossiers can be decisive to the outcome of the dossier review*

In addition to ensuring the content is fit for purpose, the responses should also be written in a polite and diplomatic style. If a question asks for information that has already been provided in the application dossier, then it helps to remember that reviewers are also only humans who are assessing a complex application

dossier under time pressure. Such a question should be responded to by providing the information again, rather than just providing a reference to where the information can be found, which would imply that the reviewer should have been more diligent in the first place. If a question indicates that the reviewer did not understand information presented in the application dossier, a different type of presentation (e.g., a figure instead of a table) may communicate the intended message more clearly, or reassess the text to see how rewording or a different rationale may improve communication of the intended message.

Conclusion

The preparation of written responses to questions received during the review of application dossiers can be decisive to the outcome of the dossier review. The main differences across regions lie with when the questions are received and the time available to respond. The challenge is not only to ensure that the responses contain relevant and focused content, but also to ensure that all team members are well prepared for responding to the questions before they arrive. Medical writers can make a substantial contribution by ensuring that appropriate responses are prepared within the stipulated timelines.

References

1. *Visit: www.fda.gov/patients/drug-development-process/step-4-fda-drug-review*
2. *Visit: www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step*
3. *Visit: www.pmda.go.jp/files/000207615.pdf*
4. *Visit: www.lexjansen.com/phuse/2014/rg/RG03.pdf*

With a PhD in Environmental Microbiology, **Douglas Fiebig** joined Hoechst (later Aventis) as a Medical Writer in 1996 and has since been involved in preparing the entire spectrum of clinical regulatory documentation. He co-founded **Trilogy Writing & Consulting** in 2002 and has prepared regulatory documents for many large and small pharmaceutical companies. Douglas' main focus has been on organising and writing CTD submission summaries, often also providing the medical writing support needed after the dossier has been submitted. He regularly runs workshops for the European Medical Writers Association (EMWA) and other organisations around the world.