How to Streamline Regulatory Authority Meetings

Streamlining meetings with regulatory authorities is a continually evolving process. But what role do briefing documents play, and what is the best way to produce these effectively?

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The development of investigational new pharmaceutical products is a long and winding road, and regulatory authorities play a role throughout the process. If sponsors wish to obtain approval for a marketing application from a particular region, they need advice and guidance from the regions' regulatory health authorities. This request for advice and guidance usually results in one or more meetings. Since these meetings aim to provide guidance and information for the sponsor to help direct and mould the product's development, they occur at critical stages of the regulatory process on the way to a submission for approval.

Briefing documents (or briefing books/packs) are the documents that support these interactions with the regulatory health authorities. Since they can shape the future of a product in a particular region, a well-written document is critical in facilitating discussions.

Meetings

Sponsors can request meetings at various stages of the product development, depending on their needs. While the meeting type terminology is different between FDA and EMA, there is considerable overlap in the kind of the meetings that can be requested between the authorities (see **Table 1, page 15**).

In the US, an applicant can request three different types of meetings (type A, B, or C) depending on the stage of clinical development (1). In the EU, the sponsor can request scientific advice or protocol assistance from the Committee for Medicinal Products for Human Use (CHMP) at much of the same stages of clinical development as in the US (e.g., EOP2 or pre submission meetings) (2). For example, if a sponsor wished to request a meeting to discuss any final aspects of the submission for marketing approval, in the EU, they would request a pre-submission meeting; in the US, the sponsor would request a type B pre-NDA meeting.

Despite their strategic importance, relatively little guidance or training is available for the preparation of briefing documents. Guidance about meetings between the health authorities and sponsors are available for both the FDA and EMA, but only the EMA provides a template for a briefing document (1, 2, 3).

Structure and Content of the Briefing Document

Most briefing documents are structured around the questions that a sponsor wishes to ask the regulatory health authority. For each question asked, the sponsor must outline their position regarding that question, and provide any background information necessary to give the authority sufficient information to assess the question/topic to be discussed.

Unlike other regulatory documents, the content of the briefing document should not be an exhaustive presentation of the entirety of information available, but rather a summary of the relevant evidence. Sponsors should consider the reason for the meeting, the topics that will be discussed, the information that has already been provided to the authority in past meetings, and the stage of development. These considerations then inform the content of the briefing document.

The typical sections of a briefing document are described below, as are suggestions and advice for each section. These standard sections should be used whenever possible

but, as indicated in the CHMP briefing document template, "if it is considered necessary to deviate from the pre-specified headings to accommodate product-specific requirements, alternative or additional headings/ sections may be considered" (3).

Product Background Summary

The first section(s) in most briefing documents is a background summary about standard product information. This section should include information on the disease or condition to be treated, the product, the development programme (at later stages of the programme, this section should focus on clinical development), regulatory status, and previous interactions with regulatory health authorities (see discussion on regional differences and **Table 2, page 16**). Information on the reason for seeking advice and the purpose of the meeting should also be included.

Questions

Questions are the core of the briefing document. Decisions regarding the topics to be discussed with the regulatory health authorities are usually coordinated by the regulatory affairs department. Questions are then typically drafted by this department, with input from multidisciplinary functions, before work starts on the briefing document.

Care should be taken when formulating questions, so as not to be vague or open-ended, and to channel the authorities towards the desired response. Questions should be clear, concise, and unambiguous. When writing the questions, a sponsor should consider that they should be asking if the authority agrees with the sponsor's position on a particular subject. The CHMP template suggests that questions should start with, "Does the CHMP agree that/with..." and this is a recommendation that should be applied to the FDA document too, e.g., "Does the Agency/FDA agree that/with…".

Questions should be ordered by discipline (for example: nonclinical, clinical, multidisciplinary) and as such, each discipline will contain subsections for every question the sponsor wishes to discuss. To help with the intricacies of a particular topic, sponsors can choose to have subquestions for questions related to the same topic.

While the available guidance does not give a limit on the number of questions that the sponsor can ask, it is important to consider the limited time allotted for

EMA Meetings	FDA Meetings
• Scientific advice • Protocol assistance • Pre-submission • Rapporteur and co-rapporteur • Regulatory strategy • PIP pre-submission • Orphan designation • Pre-submission	**Type A**: stalled product development, special protocol assessment **Type B**: pre-IND, EOP1, EOP2, pre-NDA, pre-IND **Type C**: any meeting other than types A or B

Table 1: Types of meetings

the meeting, and how extensive the debate might be on each topic. While the sponsor may not be able to discuss all questions at the meeting, written feedback for each question will be sent by the regulatory health authorities.

Sponsor's Position

Each question should be accompanied by a corresponding separate sponsor's position (or applicant or company position). This position should provide the information and data necessary to support the sponsor's argument and question. The sponsor's position can include cross-references to other sections where further information is provided. These background sections can be tailored to each briefing document and are discussed below.

The extent of the sponsor's position depends on the health authority and sponsor's preference (see discussion on regional differences), but the positions should be evidence-based. For extensive sponsor's positions (more than one page), sponsors are advised to include a short summary at the start to help guide the reader.

Background Sections

Background sections are always a necessary part of briefing documents. These sections are used if the sponsor:

A. Has any additional information that allows for a greater comprehension of the programme (e.g., summary of Phase II results at an EOP2 meeting)
B. Needs to provide supportive information that helps complement the sponsor's position and further assessment of the questions asked (e.g., providing summaries of the results of clinical pharmacology studies, when one of the questions to be asked concerns the adequacy of the clinical pharmacology package)

These sections are "neither meant to be exhaustive nor mandatory, since the relevance or applicability of each subsection may vary depending on the scope of the advice request" (3).

Annexes/Appendices

Annexes or appendices can be a good way to introduce additional information, listings, tables, figures, etc., to support the sponsor's position of each question, and will depend on the purpose of the meeting and the questions asked. These may include, but are not limited to, protocols, key publications, statistical analysis plans (study or integrated), narrative plans, clinical study report synopses, monitoring committee charters, target product profiles, and study data standardisation plan.

Regional Differences: FDA vs EMA

While EMA has a standard template for the briefing document, the layout and content of briefing documents for the FDA comes only from the sponsor's interpretation of the minimal guidance given in Section C of Chapter VII of the FDA guidance (1, 3). In reality, though, there are very few important differences between the FDA and EMA briefing documents, and they are mostly structural.

Structure of Product Information Summary

While the information provided in FDA and EMA briefing documents should be the same given a similar scope and a similar development/regulatory stage, sections may be organised differently (for an example, see **Table 2**). In the FDA briefing document, the sponsor should also provide a list of sponsor or applicant attendees (including their affiliations and titles), as well as a proposed agenda for the meeting.

EMA BRIEFING DOCUMENT	FDA BRIEFING DOCUMENT
1. Summary	1. General product information
1.1 Background information on disease	1.1 Application number
1.2 Background information on product	1.2 Product name
1.2.1 Product information	1.3 Chemical name and structure
1.2.2 Proposed indication	1.4 Proposed regulatory pathway
1.2.3 Dosing regimen	1.5 Proposed indication
1.2.4 Mechanism of action	1.6 Dosage form, route, and dosing regimen
1.2.5 Precautions and recommendations	1.7 Pediatric study plans
1.3 Quality development	2. Meeting attendees
1.4 Nonclinical development	3. Background
1.5 Clinical development	3.1 Pharmaceutical class and background
1.5.1 Clinical development plan	3.2 Development programme
1.5.2 Interactions with regulatory authorities	3.2.1 History of clinical development
1.5.3 Pediatric investigation plan	3.2.2 Interactions with regular authorities
1.6 Regulatory status	3.2.3 Substantive changes
1.7 Rationale for seeking advice	3.2.4 Current status
	4. Purpose of the meeting and proposed agenda

Table 2: Regional differences: EMA vs FDA product information summary example

Structure and Volume of Information for Questions and Background Sections

The extent of the sponsor's position can vary between the documents for the two authorities. For EMA, sponsors usually provide more information upfront and rely less on background sections, since "all key information about the topic should be sufficiently discussed, so that the Applicant position can function as a 'stand alone'" (3). Therefore, these sections can be quite extensive, though should ideally not be more than three pages. Longer sponsor positions should use subheadings to help organise the text and make it easier to comprehend. For the FDA, sponsors usually include much shorter positions, since FDA guidance indicates that questions

Checklist

- Topics to be discussed and clarified with the agency
- List of questions that will be asked. Questions should be discussed with the product development team and stakeholders, and will usually have to be approved by senior management
- Collect information on the next steps in the product development plan that has been completed so far. Collect study results, protocol synopses, and any other documents relevant to the product's development plan (e.g., Investigator's Brochure)
- Discuss with regulatory affairs any previous interactions with the regulatory health authorities regarding this product, and their impact on the briefing document
- Plan for more extensive upfront preparation: development of a briefing document usually involves more discussions and planning with different functions at the beginning than other documents, mostly due to the questions and sponsor's positions
- Timeline planning: for the FDA, the sponsor will need to submit a meeting request, which will need to include the list of questions. This request should be considered in the timelines for the development of the briefing document
- Set up meetings with relevant functions/subject matter experts to decide on the content of each section, including the sponsor's position of each question
- Schedule a kick-off meeting for alignment between functions and medical writing and for final agreement on questions (as far as possible)

Table 3: Plan of action: Briefing document-specific tasks to complete before writing starts

should include a "brief explanation of the context and purpose of the question". Most sponsors typically use high-level summaries for the position, with cross references to background sections, where further details are provided if necessary and relevant. No details are provided on this topic in the FDA guidance. However, there is generally quite a bit of variety in how this is structured (1).

Plan of Action

When planning the work on a briefing document, one should consider all the typical tasks for development of any document (such as approval of layout or planning time for quality control steps), as well as tasks that are specific to these documents (see suggestions in **Table 3**).

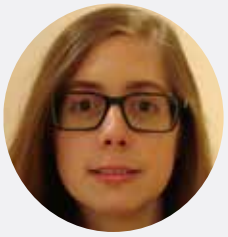
As mentioned previously, careful consideration should be given when drafting questions for the briefing document, so that the sponsor can obtain clear and precise answers. The sponsor should reflect on the risk of asking each question and the impact that an unwanted answer can have on their development goals. For example, an authority will always agree to a question from the sponsor about whether they should conduct additional studies. Sponsors should also consider the following when risk planning:

A. Different authorities might provide disparate feedback
B. Authorities may have different priorities when evaluating the product development plan

Sponsors should ensure that the content of the briefing document is appropriate, and focused on the most relevant features of the product's development. The sponsor's position and background sections should be limited to that which is relevant to each question. It is therefore crucial that the briefing document is well structured and well written, and that the relevant information is easily found and understood, to a sufficient, rather than exhaustive, detail.

References

1. *Visit: www.fda.gov/media/109951/download*
2. *Visit: www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf*
3. *Visit: www.ema.europa.eu/documents/template-form/chmp-protocol-assistance-scientific-advice-briefing-document-template_en.doc*



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