Early dialogue for a medicinal product in clinical development:

Best practice guidance for pharmaceutical companies for submission and proceeding of an early dialogue at the national level (with HAS) or at the European level (with EMA and/or other HTA bodies)

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Medical, Economic and Public Health Assessment Division


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1. Objective

The L161-37 article of the social security code gives to HAS the mission of early dialogues (ED) organisation.

The objective of an ED for a medicinal product in clinical development is to provide scientific recommendations to pharmaceutical companies on how the last phase (usually phase III) of development of a drug should be conducted in order to enable the company to provide data that will satisfy the requirements of the health technology assessment (HTA).

An ED does not constitute an assessment. Furthermore, they do not preclude the conclusions of the assessment at the time of the file submission, whether that of the Transparency Committee (TC) or, where applicable, that of the Economic and Public Health Evaluation Committee (CEESP).

For that purpose, HAS, as other HTA bodies and EMA, answer questions raised by the company about the way it is going to conduct the last phase (usually, phase III) of the development of a drug. These responses are based on the health technology assessment methods and on the relevant international guidelines in accordance with national requirements.

2. General considerations

The ED are optional, free of charge, non-binding for HAS and the companies, and confidential between the company, HAS, the other HTA bodies and EMA.

EDs can be conducted in English.

3. Methods

The general process includes the following steps:

- Request
- Admissibility
- Analysis of the dossier
- List of Questions asked by the company
- Preparation of the answers
- Face-to-Face meeting
- Report of the meeting
- Validation of the report

The ED documents are sent to the Medicines Assessment Department to the following address:

- Judith Fernandez/Anne d’Andon
- Medicines Assessment Department
  - Haute Autorité de santé
  - 5 avenue du Stade de France
  - 93218 Saint-Denis La Plaine Cedex
- j.fernandez@has-sante.fr and a.dandon@has-sante.fr

1 This guidance should be read in conjunction with Best Practice guidance for the EMA Parallel Regulatory HTA scientific Advice procedure
TABLE 1: general overview with the different steps of an ED

<table>
<thead>
<tr>
<th>Steps</th>
<th>Who?</th>
<th>How?</th>
<th>When?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Request and Briefing book version 1</strong></td>
<td>Company</td>
<td>Provide information on how the drug fulfills the criteria for an ED, proposed date for the Face to Face meeting and a word document with information listed Chapter 3.2 (5.1 Annexe 1: Composition of the Briefing book)</td>
<td>Day 0</td>
</tr>
<tr>
<td>(BB1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Admissibility</strong></td>
<td>HAS</td>
<td>According to eligibility criteria and availability of HAS to the Face to Face meeting</td>
<td>Day 15</td>
</tr>
<tr>
<td><strong>HAS comments – Pre Face to Face meeting TC</strong></td>
<td>HAS, HTA bodies, EMA</td>
<td>Word document on the list of issues of the BB1 and possibly teleconference call (TC) with the company</td>
<td>Day 30 (max 1 month after BB1)</td>
</tr>
<tr>
<td><strong>Briefing book version 2</strong></td>
<td>Company</td>
<td>Word document with modifications implementing the list of issues</td>
<td>Day 45</td>
</tr>
<tr>
<td>(BB2)</td>
<td></td>
<td></td>
<td>(15 days after the TC)</td>
</tr>
<tr>
<td><strong>Face to face meeting</strong></td>
<td>HAS, HTA bodies, EMA / Company</td>
<td>Oral presentation by the company (based on a ppt presentation sent at least 8 days before the meeting) answers to questions by EMA, HAS, HTA bodies</td>
<td>Day 90</td>
</tr>
<tr>
<td><strong>Report of the Face to Face meeting</strong></td>
<td>HAS</td>
<td>Word document based on template Chapter 3.5 Report of the face to face meeting (5.2 Annexe 2: Proposed composition of the report of the face to face meeting)</td>
<td>Day 105</td>
</tr>
<tr>
<td><strong>Validation of the report</strong></td>
<td>Company, HAS</td>
<td>Modifications</td>
<td>Day 120</td>
</tr>
</tbody>
</table>

If the timetable is not followed, HAS keeps itself the right to modify the date of the face to face meeting.
3.1 Request- letter of intent, briefing book version 1 and admissibility

At Day 0, the ED request is submitted to the Medicines Assessment Department of HAS via a letter of intent. This letter (word document) includes the brand name and the international common denomination of the drug, the claimed indication (be precised, for example state the line of treatment) and how the drug fulfills the 3 following eligibility criteria:

1) clinical development must be ongoing: between phase II (results available) and phase III (under elaboration, not yet finalised and necessarily trials not started);
2) the medicinal product must present a new way of treating a disease, a new mode of action;
3) it must cover an unmet or poorly met need.

The request also includes the briefing book version 1 (BB1). This BB1 contains a description of the disease, the indication claimed, phase II data (efficacy and safety), and the development plan for phase III (overview of the development plan and design of phase III studies) and the substantiated questions it would like to ask with the company’s position. The questions have to be as precise and as clear as possible. They should primarily address scientific issues on clinical aspects (endpoints, choice of comparator …). “For more details, see annexe 1 (5.1)”

Where applicable, an outline of the proposed method for the production of the health economics assessment is attached to this dossier.

HAS decides on the admissibility of the ED, based on:
- evidence to confirm that the product meets the three conditions set out above;
- the adequation of the question to the aim of EDs;
- the availability of the HAS team.

At Day 15, HAS confirms the admissibility of the early dialogue and proposes the date of the pre-Face to Face meeting conference call (CC) to the company.

Note: HAS keeps the right to cancel the ED if the briefing book does not contain information that fits with the letter of intent.

3.2 HAS comments, list of issues and Teleconference

At Day 30, HAS, with other agencies, will make an examination of the dossier. It may lead HAS to send to the company a list of issues or requests for additional data. If HAS has no comment, the TC is cancelled. If there are comments, a TC is organised.

The list of issues is provided by HAS by speaking with the company during the teleconference and in writing after the TC.

This list of issues contains the comments of HAS on the briefing book such as lack of data or information (does the material provided is sufficient to answer the questions), need for additional substantiation of some part of the BB, scope of the request, wording clarity of the BB, including the questions, repositioning of questions (if too wide or too narrow).

3.3 Briefing book –version 2

At Day 45, at least 15 days after the TC, the company sends a final BB (BB2) to HAS with all annexes and relevant publications. The ED will be conducted based on this version of the BB.
3.4 Face to face meeting

If significant/substantial changes are implemented into the BB2 they have to be notified as soon as possible to HAS. In this case a track changes BB2bis has to be provided at the latest three weeks before the Face to Face meeting with the reasons of the changes.

At Day 90, the Face to Face meeting aims to answer the questions raised by the company in its BB2. The company will provide its ppt presentation at least 8 days before the Face to face meeting. HAS defines the agenda of the Face to Face meeting on the basis of the questions. The usual agenda is the following:
- General considerations
- Presentation of the main points of the BB
- Questions of HAS
- Answers to questions of the company
- Conclusions

3.5 Report of the face to face meeting

At Day 105, within 15 days to a maximum period of 1 month, HAS prepares the report of the meeting. It contains:
- The context
- The participants to the face to face meeting ;
- for each question : presentation of the question from the company, advice from HAS and possible comments made at the meeting ;

This report is written in a standardised structure as detailed in Annexe 2 (5.2 Annexe 2: Proposed composition of the report of the face to face meeting):

3.6 Validation of the report

By 15 days after the Face to Face meeting the report is reviewed by the company (Day 120) and validated by HAS. It is kept by the company and HAS. It is not published.
4. Management of confidentiality and ethics

HAS personnel are bound to secrecy by their employment contracts with HAS. This obligation guarantees the confidentiality of information brought to their knowledge. No additional confidentiality agreement submitted by the manufacturer will be signed by HAS.

Where applicable, experts approached by HAS commit to confidentiality when they sign the Public Declaration of Interests (PDI). When expert(s) are chosen, their PDI and any positive and negative conflicts of interest are taken into consideration.

Experts participating in these EDs cannot participate in the assessment of the product concerned. Therefore the members of the transparency committee cannot participate in these EDs.
5. Annexes

5.1 Annexe 1: Composition of the Briefing book

The briefing book will contain the following information:

1. Clinical background and information on the target condition,
2. Presentation of the Investigational New Drug (IND): brand name DCI, mode of action, target indication,
3. Target population and claimed indication,
4. Other existing treatment options for this target indication and positioning of the IND in the therapeutic strategy,
5. Efficacy and safety data already collected for the medicinal product during the early phases of development (phases I and II, results and level of evidence),
6. Details of the planned phase III clinical trials at the very least in the form of a detailed synopsis including: design, objective, target population, comparators, endpoints, conduct, follow-up, methods of analysis and of drawing conclusions, etc, (draft or final protocol if available)
7. Where applicable, a description of the planned economic analysis, in particular concerning the assessment structuring choices (cf. HAS methodology guide, 2011). The expected effects in terms of health outcome and cost are defined. A document is available on www.has-sante.fr to provide assistance with the presentation of this information²,
8. Where applicable, publications showing the economic model, if the economic assessment is based on an existing model,
9. If so, assessments carried out by other agencies (for registration or HTA purpose),
10. Substantiated questions asked to the agency with the company's position. The questions should primarily be focused on the development plan and the design of the planned studies of the medicinal product concerned (i.e. choice of comparator, methods of administration, follow-up, endpoints, duration, etc.) but can also concern the disease treatment methods in use in France, the validity of an endpoint and the quality of life assessment methods. At this early stage of medicinal product development, the possible questions concerning the health economics study will mainly focus on the assessment-structuring methodological choices (planned type of analysis, selected and excluded comparators, perspective, time frame, population). In some cases, other aspects of the assessment could also be discussed (scope of the costs, choice of model),
11. Background information relating to each question must be provided: the context leading to the question must be presented,
12. It is advised to ask at least questions concerning study design, the choice of comparator and the endpoints should be addressed systematically.

² HAS, 2013. “Dossier préparatoire en vue d’une rencontre précoce avec le Service d’évaluation économique et santé publique” [“Preparatory dossier for an early dialogue with the Department of Economic and Public Health Assessment”] www.has-sante.fr
5.2 Annexe 2: Proposed composition of the report of the face to face meeting

<table>
<thead>
<tr>
<th>Company</th>
<th>Name/logo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of the product (INN)</td>
<td></td>
</tr>
<tr>
<td>Date of ED</td>
<td></td>
</tr>
</tbody>
</table>

1/ Context
XXX

2/ List of participants

For the company:
- 

For HAS:

For HTA bodies:

For EMA:
- 

3/ Answers to questions

<table>
<thead>
<tr>
<th>Question 1 asked by the company:</th>
<th>Answers and comments from HAS</th>
<th>Answers and comments from HTA bodies</th>
<th>Answers and comments from EMA</th>
</tr>
</thead>
</table>

And the same for the following questions