



HAUTE AUTORITÉ DE SANTÉ

EVALUATE

HEALTH TECHNOLOGIES

GUIDE

Guidance for national early dialogues on medicinal products

April 2020

Sommaire

Introduction	3
General principles	3
Confidentiality and conflict of interest management	3
Procedures	4
1. Early dialogue request	6
2. Assessment of eligibility	6
3. Submission and content of the briefing document	6
4. Choice of procedure	6
5. Examination of the dossier by the HAS	7
5.1 Standard procedure	7
5.2 Accelerated procedure	7
Annex: instructions for drafting a briefing document and its annexes	8
Abbreviations	10

Introduction

In accordance with article L. 161-37 of the French Social Security Code (CSS), one of HAS mission is to organise early dialogues with companies developing innovative medicinal products or other technologies that have a new mechanism of action, are targeting an insufficiently covered medical need and if the request is submitted before the start of pivotal clinical trials.

The objective of these early dialogues (ED) is to provide companies with recommendations on the last development phase (pivotal study/studies) and support generation of good quality evidence for proper Health Technology Assessment (HTA).

This guidance highlights ideal timelines and actions for each party undertaking a national early dialogues (i.e., consultations with HAS departments only) for a medicinal product before the start of the pivotal trial(s). Please contact the dedicated secretariat (contact.rp@has-sante.fr) should you have any question related to this procedure.

For an early dialogue with the EUnetHTA network, in collaboration with other European HTA agencies and/or in parallel with the European Medicines Agency (EMA), please refer to the [EUnetHTA guidance](#) or contact the ED secretariat (eunetha-has@has-sante.fr). If HAS participates in an early dialogue in collaboration with other European HTA agencies and/or in parallel with the EMA, the procedure will not be duplicated on a national level.

General principles

Early dialogues are optional, confidential and not binding for either HAS or the pharmaceutical companies. The recommendations provided by HAS departments reflect the state-of-the-art of medical knowledge and national requirements at the time of the early dialogue. Therefore, they do not constitute an appraisal and are not an indicator of the final appraisals reached by the Transparency Committee (CT) and/or the Commission for Economic and Public Health Evaluation (CEESP) based on future submission dossier.

During these early dialogues, HAS answers medical and medico-economic questions raised by pharmaceutical companies regarding draft protocols for pivotal studies (generally phase III trials) in accordance with HTA methods and current clinical guidelines.

Discussions and documents submitted during these national early dialogues can be in English, at the request of the pharmaceutical company seeking the early dialogue.

Confidentiality and conflict of interest management

In accordance with article R.161-84 of the CSS and HAS code of ethics, HAS staff are obliged to maintain professional secrecy. This obligation guarantees confidentiality of all the information submitted by the Applicant. No additional confidentiality agreement will be signed by HAS. HAS staff participating in these early dialogues have no conflicts of interest in relation to the technology assessed.

Experts and patients who may be involved in this early dialogue at the request of HAS, are also obliged to maintain professional secrecy in accordance with article L. 1451-1 of the French public health code and HAS code of ethics. They are selected after an internal evaluation of their declaration of interest and if no conflict of interest in relation with the technology assessed is observed.

Experts participating in these early dialogues will not be able to participate in the future assessment and appraisal process. Moreover, members of appraisals committees (CT and CEESP) can not participate in these early dialogues.

When submitting an early dialogue request, the Applicant agrees to share HAS final written recommendations with an external medical editor subject to the same confidentiality rules.

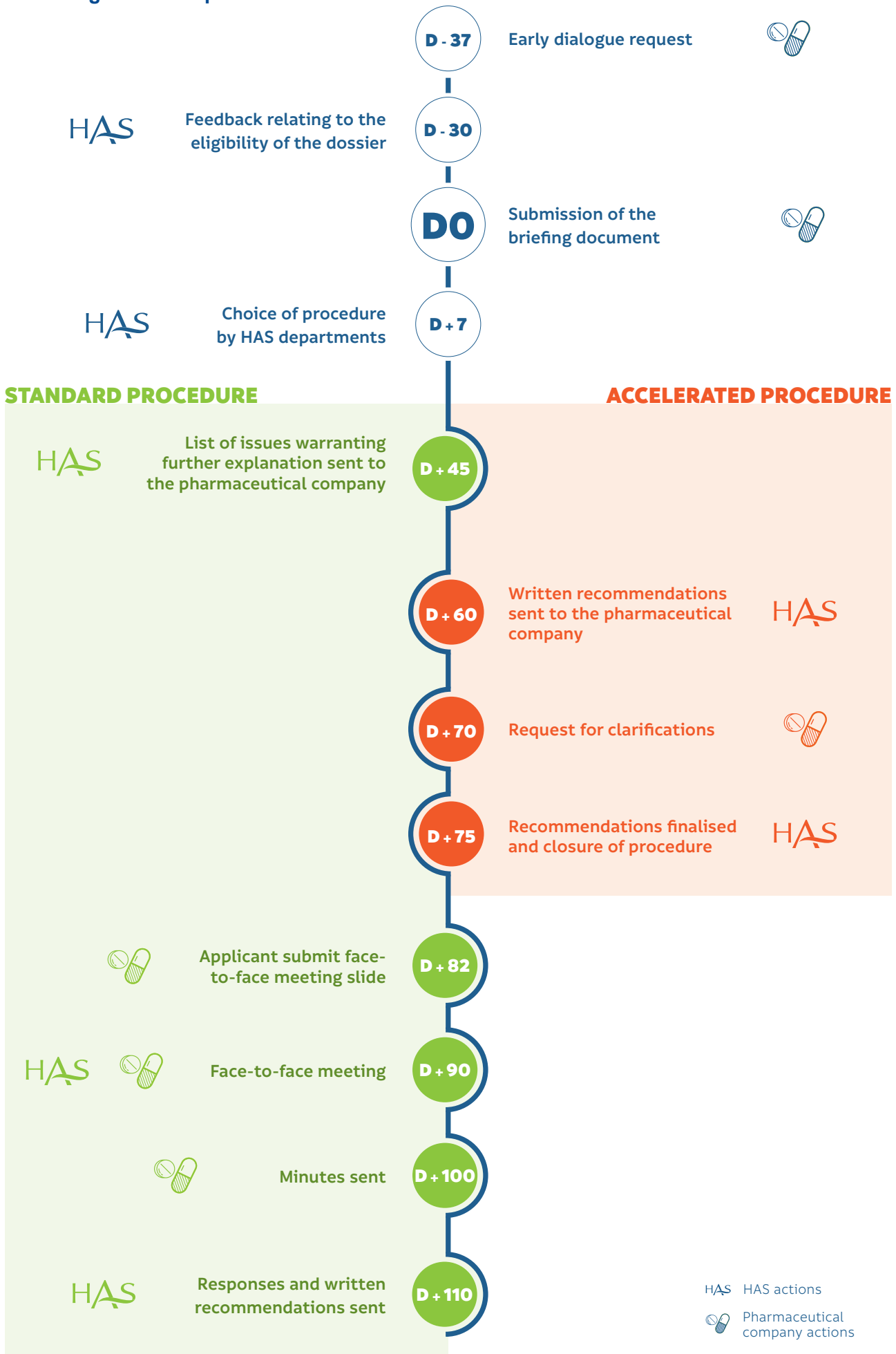
Procedures

Early dialogues can be organised following a standard procedure (with a face-to-face meeting) or an accelerated procedure (without a face-to-face meeting), as defined hereafter.

The timelines including the date of the face-to-face meeting, depends on the submission date, in accordance with the early dialogues calendar published on HAS website.

The early dialogue's step and calendar are detailed below, depending on the procedure defined by HAS.

General diagram of the procedure



1. Early dialogue request

The early dialogue request should be submitted to HAS using the online form available on the [SESAME platform](#). This request is then analysed by HAS departments to determine whether it is eligible. Only requests meeting the eligibility criteria defined in the Article L. 161-37 11° of the CSS will be accepted, i.e., requests submitted by a pharmaceutical company concerning:

- a medicinal product with a new mechanism of action in the disease, and
- targeting an indication for which there is an unmet or insufficiently covered need, and
- when the early dialogue can be finalised before the start of the pivotal clinical trials.

2. Assessment of eligibility

Within 7 days following request submission, HAS decides whether the request is eligible for an early dialogue according to the criteria above-mentioned and informs the pharmaceutical company via the SESAME platform.

3. Submission and content of the briefing document

If the early dialogue request is eligible, the company has then 30 days to submit the documents required for the early advice (briefing document) using the SESAME platform. If the company is not able to submit the briefing document at the end of this 30-day period, it shall inform HAS as soon as possible. Postponement of the procedure should then be envisaged.

The briefing document should contain a description of the disease, the medical need, the indication claimed, the data obtained during the early development phase, if available, and pivotal phase development projects. In addition, HAS encourages the company to detail projects for post-launch evidence generation if applicable, and to specify whether a French or European registry has already been identified.

The company should also indicate in the briefing document the questions HAS should address during the early dialogue. Each question should be followed by a corresponding, separate Company's position including a comprehensive justification of the chosen approach. Preliminary study reports, along with the pivotal study protocol (or synopsis) should also be submitted in the annexes.

For more information relating to the documents to be submitted, please refer to [the explanatory note appended to this document](#).

4. Choice of procedure

Based on the briefing document and considering the degree of knowledge of the disease, the complexity of its management and the clinical development proposed, HAS determines the ED procedure (standard or accelerated). The standard procedure is completed approximately 110 days after submission of the briefing document and the accelerated procedure approximately 75 days after submission of the briefing document.

HAS informs the pharmaceutical company of its decision concerning the procedure, which may include a 2-hour face-to-face meeting, as soon as possible (at the latest 7 days following the briefing document submission). If a standard procedure is decided on by the HAS, the meeting date is confirmed in accordance with the early dialogue [calendar published on the HAS website](#). The exact time of the meeting will be communicated to the company.

HAS may issue requests for clarifications relative to the documents received if necessary. In this case, a clock-stop might be decided by HAS.

5. Examination of the dossier by the HAS

5.1. Standard procedure

This procedure takes approximately 110 days following submission of the briefing document and includes a face-to-face meeting.

5.1.1 Preparation of the meeting

HAS systematically sends the company a list of issues to be addressed during the face-to-face meeting, 45 days before the meeting date.

The 2-hour meeting with HAS departments takes place on HAS premises on the date pre-specified in the [early dialogue calendar](#). Discussions during face-to-face meetings will be structured around a PowerPoint presentation prepared by the company. This presentation, along with the list of participants, should be sent to HAS via the SESAME platform at least 8 days before the date of the meeting. Following receipt of these documents, HAS will, in turn, inform the company of the list of participants on behalf of HAS.

Regarding content of this presentation, HAS recommends focusing on the list of issues. It is not necessary to reiterate the clinical background and the mechanism of action of the medicinal product if no issues are raised by HAS on these topics.

HAS prefers discussions during a face-to-face meeting, however teleconference or visioconference are possible.

If the clinical study protocol has been modified since submission of the briefing document, the company must inform HAS as soon as possible and, at the latest, 8 days before the meeting. To this end, it is invited to submit via the SESAME platform a table with three columns detailing: the old version of the protocol, the amendment(s) made and the rationale for the change(s).

5.1.2 Finalisation of the procedure

The company is responsible for taking the minutes of the meeting and sending these to HAS within 10 days after the meeting. These minutes will be reviewed but not be validated by HAS. Minutes will not be published.

HAS sends written final recommendations in response to the questions raised by the company 20 days after the face-to-face meeting, thereby closing the procedure (i.e., on D+110 after the date of submission of the briefing document). If one or several patients were consulted by the HAS, the minutes of this consultation will be appended to the final recommendations (prior agreement from patient[s] needed).

5.2. Accelerated procedure

This procedure takes approximately 75 days following submission of the briefing document and does not include a face-to-face meeting.

Two months after submission of the briefing document, HAS sends the draft written recommendations to the Company in response to the questions raised by the Applicant in the briefing document. The Company has then 10 days to submit requests for clarifications on this document if needed. In response to these requests for clarifications, HAS sends written the final recommendations, thereby closing the procedure.

If the clinical study protocol has been modified since submission of the briefing document, the company must inform HAS as soon as possible and, at the latest, 10 days before the written responses are sent. To this end, it is invited to submit via the SESAME platform a table with three columns detailing: the old version of the protocol, the amendment(s) made and the rationale for the change(s).

If one or several patients were consulted by HAS, the minutes of this consultation will be appended to the final recommendations (prior agreement from patient[s] needed).

Annex: instructions for drafting a briefing document and its annexes

General outline of the briefing document and its annexes

When drafting the briefing document, it is recommended to follow the structure described below:

Table of contents

Lists of figures and tables

List of abbreviations

1. Presentation of the target disease

a. Aetiology, epidemiology and disease symptoms and burden

b. Current care pathway

c. Other medicinal products undergoing development in this disease (including compassionate use programmes)

2. Presentation of the medicinal product undergoing clinical development

a. Mechanism of action

b. Summary of ongoing or completed clinical studies

c. Study protocol that is the subject of the early dialogue (inclusion and exclusion criteria, endpoints, patient reported outcomes, sample size estimation, statistical analyses, etc.)

d. Choice of PROs or PRO measures (PROMs)

3. Presentation of the envisaged medico-economic assessment (optional)

4. Pharmaceutical company questions for the HAS

a. Questions related to the population included in the clinical trial and its generalisability with respect to the claimed indication

b. Questions related to the clinical trial comparator and/or other clinically relevant comparator(s)

c. Questions related to primary and secondary endpoints (including PROs)

d. Questions related to the design of the clinical trial and/or the statistical analysis

e. Questions related to the data collection envisaged after the MA is granted (optional)

f. Questions related to the medico-economic assessment (optional)

g. Other questions (optional)

Each question must be followed by a corresponding, separate Company's position including a comprehensive justification of the chosen approach. The Company's position regarding PROs must include a review of the literature relating to existing PROs in the disease, along with justification of the appropriateness of the questionnaire(s) chosen and the frequency of collection of these data.

Annexs :

1. Clinical study protocol that is the subject of the early dialogue.
2. Descriptions of ongoing or future clinical studies in other indications.
3. Diagram summarising the clinical development schedule and the regulatory steps (all indications).
4. Reports of from early dialogues performed with regulatory agencies or other HTA bodies if applicable.
5. Opinion of the CAT and/or COMP if relevant.
6. Bibliography (each referenced article must be submitted in PDF format).

Recommendations on the wording of the questions

It is recommended that the number of questions be limited (10 maximum) in order to focus the discussion on the relevant aspects of the dossier. Questions concerning the future appraisals of the CT and the CEESP (clinical benefit/clinical added value and methodological reservations concerning the medico-economic assessment) will not be considered by the HAS, in accordance with the general principles of early dialogues (see page 3). Furthermore, as the existence of a medical need is included in HAS eligibility assessment, these questions are out of the scope of an early dialogue

Questions on post launch evidence generation are optional but recommended if relevant in the clinical development plan. In this case, the Company should detail its plan for post-registration studies and list French or European registries that may already exist.

Abbreviations

CAT: Committee for Advanced Therapies

CEESP: *Commission évaluation économique et de santé publique* (Commission for Economic and Public Health Evaluation)

COMP: Committee for Orphan Medicinal Products

CT: *Commission de la Transparence*

CSS: *Code de la sécurité sociale* (French Social Security Code)

ED: early dialogue

EUnetHTA: European Network for Health Technology Assessment

HAS: *Haute Autorité de santé* (French National Authority for Health)

HTA: Health Technology Assessment

Find all of our works on
www.has-sante.fr

