

|                                               | <b>Procedure description for Pharmaceuticals</b><br><b>EUnetHTA multi-HTA Early Dialogues</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| <b>DAYS</b><br><small>(calendar days)</small> | <p><b>ACTIONS concern:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>ED applicant</b> (company)</li> <li>▶▶ <b>European Medicines Agency (EMA)</b> is invited to be an observer at the f2f meeting and TCs prior to the f2f meeting.</li> <li>▶▶ <b>HTA body (HTAB) coordinator</b> (either HAS or G-BA, specified for each ED), will also serve as <b>chair</b> for the specific ED face-to-face (f2f) meeting.</li> <li>▶▶ <b>HTAB representatives organized in an ED committee (HEDC)</b>, participating in specific ED. Participation in the respective ED is on a voluntary basis, trying to accommodate the company's preferences if possible.</li> <li>▶▶ <b>Minute taker:</b> volunteering member of the HEDC, responsible for taking minutes of the f2f discussion.</li> <li>▶▶ <b>HTAB Rapporteurs</b>, coming out of the HEDC, one or two, depending on ED; at least one of them in the case of two should be an experienced HTAB representative. HTAB Rapporteurs are being supported by the HTAB coordinator with respect to procedural issues.</li> <li>▶▶ <b>Senior scientific officer</b> of the JA3 Directorate: will participate as observer in ED f2f meeting to ensure link to other work packages.</li> <li>▶▶ <b>Standing Committee (SC):</b> The EUnetHTA standing working party of HTABs for the conduct of Early Dialogues for pharmaceuticals.</li> </ul> |
| <b>D -65-<br/>D -60</b>                       | <p style="text-align: center;"><b>Letter of Intent/Product selection:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>Company</b> submits the letter of intent to the <b>HTAB coordinator</b> (at the latest at D -65)</li> <li>▶▶ <b>Selection of product by WP5A LP/CoLP</b> (general eligibility check; i.e., regarding the prospective nature of the requested advice).</li> </ul> <p style="text-align: center;"><b>HTAB Coordinator appointment for ED:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>LP/CoLP decide who is coordinating specific ED</b></li> </ul> <p style="text-align: center;"><b>Formation of HTAB ED committee (HEDC):</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>HTAB coordinator</b> transmits the letter of intent to all HTABs</li> <li>▶▶ <b>HEDC for the particular product:</b> participation of HTABs is voluntary. The company can express their interest in particular HTABs; however, it cannot be guaranteed that all of those HTABs will be participating.</li> <li>▶▶ <b>HTAB coordinator</b> emails the decision on the eligibility of the product to the <b>HEDC</b>, following predefined criteria for eligibility.</li> </ul>                                                                                                                                                                                          |

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|                        | <b>Procedure description for Pharmaceuticals</b><br><b>EUnetHTA multi-HTA Early Dialogues</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| <b>D -30<br/>START</b> | <p style="text-align: center;"><b>Draft briefing book:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>Company</b> submits the draft briefing book, annexes and references to the <b>HTAB coordinator</b><sup>1,2</sup>.</li> <li>▶▶ <b>HTAB coordinator</b> communicates the draft briefing book, annexes and references to <b>HEDC</b>.</li> <li>▶▶ <b>HTABs of the HEDC</b> check the document for completeness and clarity of information, including points that need further justification from the company (until D -15).</li> </ul>                                                                                                                                                                                                                                                                                            |
| <b>D -15</b>           | <p style="text-align: center;"><b>Written request for clarification and further justification of planned methods etc.:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>HTABs of the HEDC</b> send a written request for clarification, missing information and further justification to the <b>HTAB coordinator</b>.</li> <li>▶▶ <b>HTAB coordinator</b> compiles <b>HTAB's</b> written request for clarification in a single document, which is the <i>consolidated request for clarification</i>. Distribution of the consolidated list to the <b>HEDC</b>.</li> <li>▶▶ <b>HTAB coordinator</b> sends the consolidated request for clarification to the company with administrative and specific <i>instructions for the company to prepare the final briefing book</i>. TC with the company (unless decided otherwise).</li> </ul> |
| <b>D 0</b>             | <p style="text-align: center;"><b>Final briefing book:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>Company</b> sends to <b>HTAB coordinator</b> the final briefing book with responses to the request for clarification integrated in 'track changes' mode. In addition, a clean copy of the briefing book (word document) is provided by the company.</li> <li>▶▶ <b>HTAB coordinator</b> forwards the final briefing book to <b>HEDC</b>.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                            |
| <b>D 0 to<br/>D 25</b> | <p style="text-align: center;"><b>Draft written position by HTA bodies:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>HTABs</b> provide draft written position <i>on each question</i> of the company, indicating which of the questions raise particular concerns (= is a potential key issue) that deserve specific attention from the company.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>D 25</b>            | <ul style="list-style-type: none"> <li>▶▶ <b>HTABs</b> send their draft written positions, including the identified potential key issues raised by the proposed development plan to the specified <b>HTAB coordinator</b>. These positions should include an indication of how fixed this position is (0 = non-negotiable, 1 = maybe flexible, 2 = flexible). <b>HTAB coordinator</b> distributes them among the <b>HEDC</b> members.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                           |

<sup>1</sup> A unique electronic address will be provided by EUnetHTA for all incoming/outgoing electronic exchanges related to the Early Dialogue activity.

<sup>2</sup> The use of a secure link system (for authorized personnel only) is necessary to ensure proper transmission of large files and the confidentiality of sensitive documents.

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| <b>D 30</b>                                                                                   | <ul style="list-style-type: none"> <li>▶▶ <b>HTAB coordinator</b> organises and leads an e-meeting with the <b>HEDC</b> for the ED to discuss the draft written positions.</li> <li>▶▶ The purpose of this e-meeting is:               <ol style="list-style-type: none"> <li>1) to identify the questions for which there is a shared position amongst HTA bodies</li> <li>2) to discuss questions for which the answers of the HTA Bodies diverge, to understand the reasons for divergence and attempt to reach consensus and</li> <li>3) identify and discuss common key issues.</li> <li>4) In addition, a discussion on whether the diverging requirements can still be accommodated within one trial or not, should be accommodated.</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>D 32</b>                                                                                   | <ul style="list-style-type: none"> <li>▶▶ Following the e-meeting, the <b>HTAB rapporteur</b> <ul style="list-style-type: none"> <li>- consolidates the list of key issues and sends it to the <b>HTAB coordinator</b></li> <li>- defines which questions will receive a consolidated answer (= answer for which there is a shared position among HTABs) and which deserve individual answers by every partner. The rapporteur sends this information to the <b>HTAB coordinator</b>.</li> <li>- starts drafting written answers to the questions for which there is a shared position among HTABs, to be finished by D 50.</li> </ul> </li> <li>▶▶ <b>HTAB coordinator</b> then               <ul style="list-style-type: none"> <li>- sends the list of key issues to the company.</li> <li>- provides the information on which answers will be consolidated vs. individual ones to the <b>HEDC</b> for the respective ED.</li> </ul> </li> <li>▶▶ <b>HTABs of the HEDC</b> start individually drafting their answers to those questions for which there was no consensus, to be finished by D 50 and to be sent to both <b>HTAB rapporteur</b> and <b>HTAB coordinator</b>.</li> </ul> |
| <b>D 45</b>                                                                                   | <p><b>Company's response to list of key issues:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>Company</b> sends their written responses (if applicable) to the key issues raised by the <b>HEDC</b> to the <b>HTAB coordinator</b>.</li> <li>▶▶ <b>The HTAB coordinator</b> distributes the company's written answers (if applicable).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>D 50</b>                                                                                   | <p><b>HTA draft written answers:</b></p> <ul style="list-style-type: none"> <li>▶▶ The <b>HTAB rapporteur</b> compiles draft written answers to all questions from the briefing book raised by the company, validated by the <b>HTAB coordinator</b>.</li> <li>▶▶ <b>HTAB coordinator</b> sends the compiled draft written answers to the <b>HEDC</b>.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                             | <p style="text-align: center;"><b>Procedure description for Pharmaceuticals</b><br/><b>EUnetHTA multi-HTA Early Dialogues</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <p><b>D 55 /<br/>D 59</b></p>               | <ul style="list-style-type: none"> <li>▶▶ <b>HTAB coordinator</b> holds a conference call with the <b>HEDC</b> for a discussion of the draft written answers and company's response to key issues. Discussion should include the possibility to reach further convergence</li> <li>▶▶ <b>Company</b> sends power point presentation to <b>HTAB coordinator</b>, 4 full working days before f2f meeting. <b>HTAB coordinator</b> distributes the slides amongst <b>HEDC</b>.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p><b>D 60</b><br/><b>Mee-<br/>ting</b></p> | <p style="text-align: center;"><b>Face-to-face meeting:</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>The ED meeting is a 1-day meeting dedicated to 1 ED procedure. The meeting is generally organised as follows:</b></li> </ul> <p>It is organised and hosted by the <b>HTAB coordinator</b>. The <b>Senior scientific officer (directorate)</b> is observing the meeting.</p> <ul style="list-style-type: none"> <li>▶▶ <b>Morning session: discussion among HTA bodies only:</b></li> </ul> <p>Two-hour session to refresh and possibly update common views (general opinion) and differences in HTAB's positions. Chaired by <b>HTAB coordinator</b>.</p> <ul style="list-style-type: none"> <li>▶▶ <b>Afternoon session: f2f meeting of HEDC with the company:</b></li> </ul> <p>Three to four-hour meeting chaired by the <b>HTAB coordinator</b>. The nature of the meeting should be interactive.</p> <p>The company addresses key issues that were identified by the EDC. The <b>HTAB rapporteur(s)</b> and, as appropriate, other EDC members, present answers to all questions, indicating whether there was convergence, and if so, of which HTABs, and where there was divergence among the answers.</p> <ul style="list-style-type: none"> <li>▶▶ <b>Final discussion on lessons learned (HEDC only):</b></li> </ul> <p>This discussion should be both ED specific, as well as referring to more general procedural aspects, with the aim of continuously improving the procedure.</p> |
| <p><b>D 70</b></p>                          | <p style="text-align: center;"><b>HTAB's final written answers:</b></p> <p><b>The HTAB rapporteur, supported by the HTAB coordinator, produces final written answers for the company.</b></p> <ul style="list-style-type: none"> <li>▶▶ <b>Each HEDC member for that ED</b> reviews the final written answers in order to ensure correctness. Endorsement of the final written answers only by those HTABs that were involved in the particular ED (i.e., were members of the HEDC).</li> <li>▶▶ <b>HTAB coordinator</b> sends the final document to both the HEDC and company as a final deliverable.</li> </ul> <p>Possibility for addenda to the written answers in case of new issues arising during the course of f2f meeting</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |