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2 EMA/109608/2014  
3 Human Medicines Development and Evaluation

## 4 Best Practice guidance for Pilot EMA HTA Parallel Scientific 5 Advice procedures

6 For consultation

### 7 Table of contents

8	<b>Abbreviations</b> .....	<b>2</b>
9	<b>1. Draft Process</b> .....	<b>2</b>
10	1.1. Introduction.....	2
11	1.2. Principles .....	3
12	1.3. Phases of the EMA HTA Parallel Scientific Advice process .....	4
13	1.3.1. Pre-notification phase .....	4
14	1.3.2. Pre-validation Phase .....	5
15	1.3.3. Meeting Phase.....	7
16	1.4. Advice format .....	8
17	1.5. Amendments to development plans .....	8
18	1.6. Follow up procedures .....	8
19	1.7. Example of procedural Timetable.....	8
20	<b>2. Questions for public consultation on the Process for EMA-HTA Parallel</b>	
21	<b>Scientific Advice</b> .....	<b>9</b>
22	<b>3. Annex Briefing Document Template</b> .....	<b>10</b>
23		



## 24 **Abbreviations**

25	AIFA	Agenzia Italiana del Farmaco
26	AQUAS	Agency for Health Quality and Assessment of Catalonia
27	CHMP	Committee for medicinal products for human use
28	EC	European Commission
29	EMA	European Medicines Agency
30	EUnetHTA	European Network for Health technology Assessment
31	G-Bba	Gemeinsamer Bundesausschuss
32	HTA	Health Technology Assessment
33	HAS	Haute Autorité de Santé
34	HVB	Hauptverband der österreichischen Sozialversicherungsträger
35	HTABs	Health Technology Assessment Bodies
36	LOI	Letter of Intent
37	NICE	National Institute for Health and Care Excellence
38	SAWP	Scientific Advice Working Party
39	SEED	Shaping European Early Dialogues
40	TC	Teleconference
41	TLV	Tandvårds- och Läkemedelsförmånsverket

## 42 **1. Draft Process**

### 43 **1.1. Introduction**

44 As the first step to market access, a new medicine requires a marketing authorisation from a medicines  
45 regulatory agency. The second step prior to enabling patient access to a new therapeutic option  
46 increasingly involves the assessment of its usefulness to the healthcare system that lies with a payer  
47 or healthcare-guidance organisation, and the Health Technology Assessment Bodies (HTABs) that  
48 advise them.

49 A strong interaction between regulators and HTABs is critical to enable innovation to reach patients,  
50 and ultimately for the benefit of public health. There is a clear need to initiate early dialogue between  
51 medicines developers, regulators and HTABs to discuss and agree on a development plan that  
52 generates data that both parties can use to determine a medicine's benefit-risk balance and value. For  
53 this document, and the purposes of Parallel Scientific Advice, the European Medicines Agency (EMA) is  
54 the European Union body responsible for coordinating the existing scientific resources put at its  
55 disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal  
56 products, including the provision of scientific advice for regulatory ends.

57 The HTABs operate at a local or national level under specific local or national rules. See below for  
58 Products and indication in scope for participating HTABs.

59 The following process has been drafted based on the experience to date since 2010 with the help of  
60 multi-stakeholder working group comprising the European Medicines Agency (EMA) and regulatory  
61 National Competent Authority delegates from the EMA Scientific Advice Working Party (SAWP), with  
62 HTA representatives from NICE, AIFA, G-Ba, TLV, as the HTAs who have undertaken such procedures  
63 most frequently. Other HTABs who have undertaken EMA HTA Parallel Scientific Advice procedures  
64 have also been consulted including AQUAS, HAS, and HVB.

65 Since 2010, the EMA has put in place a pilot project of Parallel Scientific Advice with the participation  
66 of the above mentioned HTA bodies that allows developers to receive simultaneous feedback from both  
67 regulators and national HTA bodies on their development plans for new medicines. Further input on the  
68 draft process was received during the EMA HTA workshop on Parallel Scientific Advice 26th November  
69 2013.

70 In addition to this initiative, HTABs have performed several multi-HTABs early dialogues in the  
71 framework of the EUnetHTA Joint Actions (JA) 1 and 2, and EMA was invited to participate as observer  
72 in the multi-HTABs early dialogues of EUnetHTA JA2. In addition, since September 2013, under the  
73 coordination by HAS, 14 HTABs have initiated the SEED (Shaping European Early Dialogues for health  
74 technologies) project, financed by the EU Commission, to perform 10 additional multi-HTABs early  
75 dialogues and explore possible scenarios for conducting early dialogues in the future. EMA is  
76 associated to the SEED project and will take part in three of these dialogues as EMA SEED parallel  
77 advice procedures. Both the results of EUnetHTA JA2, the SEED project as well as the results of EMA  
78 HTA Parallel Scientific Advice pilot (the draft process under consideration in this document) and the  
79 public consultation will be carefully taken into account and assessed to lead possibly to a revised  
80 workflow/ process to best meet the objective of the Early Dialogue exercise in the medium term.

## 81 **1.2. Principles**

82 This Parallel Scientific Advice with EMA and HTABs will continue as a pilot project. This document sets  
83 out the best practice for all parties, including HTABs, EMA and Applicants undertaking an EMA HTA  
84 Parallel Scientific Advice procedure under this pilot. This best practice guide highlights ideal timelines  
85 and actions for each party.

86 EMA HTA Parallel Scientific Advice is a multi-stakeholder procedure. As a multi-stakeholder procedure,  
87 communication between project managers of all stakeholders is important to ensure agreement and  
88 clarity on ownership of different actions.

89 Each participating body adheres to the roles and responsibilities under their respective remit.

90 The process is confidential.

### 91 **Products and indication in scope; EMA**

92 No restriction in indications is foreseen from the EMA perspective beyond those products should be in  
93 scope for standard EMA scientific advice, qualification advice, qualification opinions or Broad advice on  
94 non-product specific areas. Advice may be requested for all medicinal products for use in humans, (as  
95 defined in Directive 2001/83 (as amended)), irrespective of the medicinal product's eligibility for the  
96 centralised procedure, including advice on the design of studies and trials to support quality, safety  
97 and efficacy of a medicinal product at all stages of the product lifecycle. This may include post-  
98 authorisation safety and efficacy studies and risk management planning incorporating risk minimisation  
99 measures. For the EMA, the Scientific Advice or Protocol Assistance is provided pursuant to Article 57  
100 (1.n) of Regulation (EC) No 726/2004). The scientific advice provided by the EMA is adopted by  
101 Committee for Medicinal Products for Human Use (CHMP) having been elaborated through the Scientific

102 Advice Working Party (SAWP). SAWP members may be CHMP members or European experts from  
103 regulatory authorities or academia, and are supported by the EMA secretariat. See the published EMA  
104 Scientific advice Guidance document for further details.

## 105 **Products and indication in scope; HTABs**

106 Applicants should familiarise themselves with the scope, prerequisites and activities of participating  
107 HTABs. Available information has been collated by HTAs participating in the pilot, and is available on  
108 demand from EMA Scientific Advice Office. It should be noted that *some* HTA agencies may charge fees  
109 for participation in Scientific Advice in addition to those fees charged by the EMA Scientific Advice. It is  
110 the choice of the Applicant which HTABs to select and approach. If considering more than 5 HTABs,  
111 additional discussion with an EMA Scientific Advice Officer is recommended. There is no obligation for  
112 invited HTABs to participate in a specific procedure.

113 A common briefing document is used; each question can be addressed to the EMA, or the HTABs alone,  
114 or to both. Use of the associated briefing document template is strongly recommended. See Annex.

115 The advice provided by each stakeholder is not legally binding and provided in line with their usual  
116 practice.

### 117 **1.3. Phases of the EMA HTA Parallel Scientific Advice process**

118 Scientific advice with HTABs and the EMA has a pre-notification phase, a pre-validation phase and a  
119 meeting phase. See Figure 1 below for the overview and actions by each party in parallel.

#### 120 **1.3.1. Pre-notification phase**

121 It is strongly recommended that Applicants engage early in informal discussions with HTABs and EMA  
122 to pre-notify their intention for procedure, the product, timescale, and which stakeholders are  
123 expected to participate well in advance of sending a formal Letter of Intent to the EMA.

124 When the preferred date of the face to face meeting is known by the Applicant, the Applicant requests  
125 a confirmation from the EMA regarding the agreed date, time and place of the Face to Face meeting.

126 It is recommended to pre-notify the EMA approximately 6 months before the intended Face to Face  
127 meeting in the event a pre-validation phase with a TC is anticipated. However, 4 months could be an  
128 adequate period for pre-notification where a shortened pre-validation phase is anticipated. The  
129 Applicant is responsible for sending this EMA date confirmation to the HTABs they wish to invite.

130 The EMA date confirmation should be received by the HTABs at the latest 3 months in advance of the  
131 Face to Face meeting for organisational purposes.

132 Additional HTABs are able to join the procedure in later phases if they are agreeable.

133 HTABs may also participate as observers only following invitation by the Applicant.

134 EMA can brief participants on the expected process.

135 The EMA can provide contact details of the HTABs to the Applicant.

136 The pre-notification phase ends when the Applicant sends the Letter of Intent to the EMA once all  
137 parties have confirmed their participation. The Letter should be sent in line with published EMA  
138 scientific advice timetables for a 70 day procedure (with or without a pre-submission meeting).

## 139 **Communication and coordination during a procedure**

140 It is preferable to have one principal point of contact (with a backup) for all stakeholders. The Letter of  
141 Intent should be sent to EMA with the email and phone contact details of all participating stakeholders.

142 The EMA Scientific Advice Officers and HTAB project managers should be kept up to date with any  
143 changes/developments. E.g. new HTABs/ contact changes.

144 At an early stage, HTABs and EMA may consider the clinical experts required for participation in the  
145 procedure and Face to Face meeting. Two Co-ordinators who are members of the EMA Scientific Advice  
146 Working Party (SAWP), from national regulatory agencies are appointed to lead their respective  
147 assessment teams for the SAWP. For the EMA, conflict of interest of experts and patient  
148 representatives will be handled in line with standard EMA policies.

149 Project managers (EMA, HTABs and Applicant) will consult early on a draft timetable (EMA will provide  
150 a first draft) to be agreed for key dates in the parallel procedure (see example of draft time table of  
151 dates below). This should be communicated as early as possible to all stakeholders to facilitate work  
152 planning and co-ordination.

153 Calendar meeting requests will be sent by EMA to HTABs and other regulatory participants.

154 EMA uses Eudralink - a secure system for sending /receiving documents between parties in its in house  
155 procedure. The Applicant should clarify with HTABs on their preferred method of sending and receiving  
156 documents.

157 The Applicant is responsible for sending any Applicant documents to the HTABs and to the EMA parties.

158 Whilst there is some flexibility in arranging deadlines, it is advisable to adhere to timelines to ensure  
159 the optimum time is available to assessors and reviewers of documents.

160 Document version control and numbering is essential to ensure all parties have the appropriate  
161 document at the correct time.

### 162 **1.3.2. Pre-validation Phase**

163 There are different options for Applicants to consider which will allows some flexibility in the pre-  
164 validation phase.

165 Option 1: 60-80 day pre-validation phase allows a possible teleconference (TC) between HTABs, EMA  
166 and the Applicant. This would be most suitable for inexperienced Applicants or very complex or  
167 controversial programs. Invited HTABs reserve the option to participate in the TC or comment via  
168 email, further to review of the draft briefing document. The procedure timetable will be based on the  
169 EMA published scientific advice timetables for a 70 day procedure with a pre-submission meeting.

170 Option 2: ~45 day pre-validation phase with no TC, but with written comments from EMA and HTABs  
171 where necessary for the optimisation of the draft submission. The procedure timetable will be based on  
172 the EMA published scientific advice timetables for a 70 day procedure without a pre-submission  
173 meeting.

174 In case of option 1 and 2, the first draft of the briefing book should be sent to the EMA in line with the  
175 agreed timetable for the procedure.

176 For option 1: A pre-validation teleconference (TC) will take place approximately 2-3 weeks after the  
177 briefing book has been received by all parties; involving the EMA, HTABs and Applicant. The EMA will  
178 arrange this TC upon agreement of the timetable and send TC details to all parties.

179 The Applicant circulates the pre-validation presentation with numbered slides covering briefly the  
 180 background, the questions and Applicant positions, to all participants at least 48 hours before the TC  
 181 including a list of Applicant's participants.

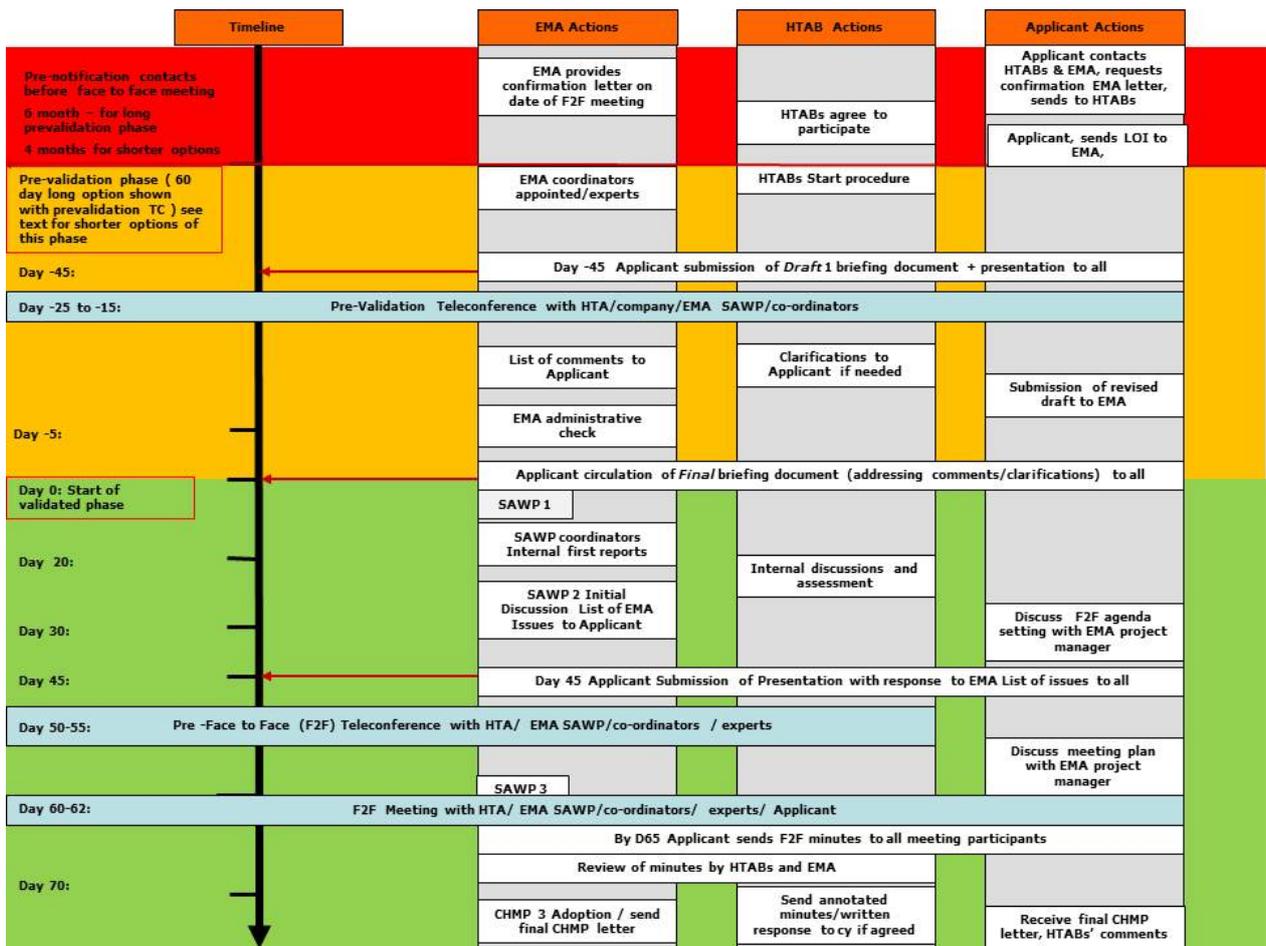
182 The aim of the pre-validation TC is to discuss the scope, wording and clarity of the questions, and  
 183 whether the material provided in the briefing package is sufficient to answer the questions posed.  
 184 Reviewing the choice of questions, such as questions on population, comparator etc at an early stage is  
 185 considered important as the procedure will not be able to expand to add new questions at a later date.

186 After, the pre-validation TC, the EMA will send their regulatory comments on the package in writing  
 187 within 2 days. HTABs may send comments on the package/seek clarifications individually to the  
 188 Applicant after the pre-validation TC according to their usual practice. It is considered helpful if  
 189 comments are shared among participants.

190 For Option 2: comments from the EMA and HTABs will be provided in writing as needed allowing  
 191 sufficient time to revise the draft document, and in line with the agreed procedural timetable.

192 In either option, the Applicant sends a revised final briefing document, addressing the EMA comments  
 193 and HTAB points of clarification in the agreed time frame to the EMA contacts, and to the HTABs in the  
 194 manner agreed.

195 The pre-validation phase ends with the submission of the final document. This is timed to coincide with  
 196 the SAWP meeting 1 (the formal procedure start) in standard EMA scientific advice. The EMA will  
 197 conduct an administrative check to ensure the briefing pack is fit for purpose i.e. that all annexes and  
 198 references are present.  
 199



200 **Figure 1** Overview of process and actions by each party in parallel showing the longer pre-validation  
 201 phase.  
 202

### 203 **1.3.3. Meeting Phase**

204 In the EMA regulatory process, the scientific advice working party (SAWP) discusses the first reports  
205 (preliminary views) at the SAWP 2 meeting and generates a List of Issues by the end of SAWP 2. EMA  
206 sends this List of Issues to the Applicant. The Applicant is strongly recommended to send the EMA List  
207 of Issues to the HTABs. HTABs consider it very helpful to receive this document. This will facilitate the  
208 discussion during the Face to Face meeting indicating the focus of regulators' discussion.

209 HTABs' in-house processes: each HTAB proceeds with their internal assessment and discussion in  
210 accordance with national policies and requirements.

211 The Applicant is advised to contact the EMA Scientific Advice Officer to discuss the format of the Face  
212 to Face meeting.

213 The Applicant should send the presentation for the Face to Face meeting within 2 weeks of receipt of  
214 the List of Issues - to the EMA and to the HTABs, together with any written responses if these are  
215 requested.

216 The presentation can include a very brief introduction, rationale and status of the program; all the  
217 briefing document questions and key points of the Applicant can be addressed. Tables and figures are  
218 useful. The issues raised by the EMA can be intercalated into the presentation with the relevant  
219 question but this can be discussed with the EMA scientific officer. The introduction, rationale and status  
220 of the program section should be very brief to maximise the time for the questions and discussion. It is  
221 usual to pause after each question/issue for discussion. Once sent to the meeting participants,  
222 according to the agreed timelines, the presentation should not be substantially amended by the  
223 Applicant.

#### 224 **Amended development plans triggered by the EMA List of Issues or external factors.**

225 These can be accommodated during the meeting phase. However, to facilitate sufficient time for review  
226 of the amended development plan, it is stressed that the Applicant should advise all parties of their  
227 intention to submit it as soon as this is decided. The plan must be received by all parties, at the latest,  
228 by 2.5 weeks before the Face to Face meeting together with: the presentation for the Face to Face  
229 meeting, a clear comparative table of changes in the plans, and justification for the changes. Any  
230 substantial changes to the development plan submitted past this date cannot be addressed within the  
231 Face to Face meeting or minutes, at least by some HTAs.

232 The EMA will arrange a closed preparatory TC with the HTABs. This will be arranged to take place after  
233 the Applicant sends the responses to the List of Issues/presentation in order to review respective  
234 preliminary positions. The purpose of the Pre-Face to Face TC is to identify critical divergences  
235 between HTABs and the EMA on the proposed development plan. Feedback on possible divergences will  
236 be communicated to the Applicant in advance of the Face to Face meeting by the EMA Scientific Advice  
237 Officer to facilitate preparation for the meeting, with the caveat that important divergences may also  
238 be discerned during the Face to Face meeting, and that this feedback does not prejudge the Face to  
239 Face meeting.

240 The Face to Face meeting will normally have 2 co-chairs: one from EMA/SAWP and one from the  
241 HTABs. Regarding the choice of HTAB chair, this will rotate amongst the HTABs and will be agreed  
242 between the HTABs, on a case by case basis. The EMA Scientific Advice Officer will liaise with  
243 participating HTABs, and the chair should be agreed 4 weeks in advance of the Face to Face meeting.

244 The Meeting time is approximately 4 hours including a short break. The Applicant can prepare the  
245 agenda allocating time according to priorities, sending this with the presentation and list of Applicant  
246 attendees. Hard copies are not required.

247 HTABs are asked to send their final list of attendees to the EMA also in advance of the meeting. The  
248 EMA will circulate a final list of regulatory participants 2 days in advance of the Face to Face meeting.  
249 The meeting is hosted at EMA premises.

250 The inclusion of patient representatives in the Face to Face meeting is encouraged; briefing of chairs,  
251 and patients regarding the purpose and role of the meeting and of patient representation is essential.  
252 Additional time or facilities required by patients should be considered in these cases.

253 During the Face to Face meeting; the views of each stakeholder should be clearly represented on each  
254 issue.

#### 255 **1.4. Advice format**

256 The Applicant is expected to send detailed minutes of the Face to Face meeting, attributing individual  
257 views to the respective stakeholder, within 5 days to all participants who will review these. In this  
258 respect, minutes should reflect the views for each HTAB participating to the Face to Face meeting  
259 discussion.

260 The EMA final advice letter contains CHMP regulatory advice only. HTAB feedback is provided directly  
261 to companies during the Face to Face meeting, according to HTAB normal practice or by annotating the  
262 Applicant's minutes, or by providing written answers. For some countries, minutes do not replace the  
263 national advice protocol for official purposes. See the collated HTAB information referred to above.

#### 264 **1.5. Amendments to development plans**

265 See above in meeting phase.

#### 266 **1.6. Follow up procedures**

267 A procedure can be a follow-up to an earlier Parallel Scientific Advice procedure for the same  
268 indication. There is no time window during which this has to be completed. It would be expected that  
269 follow up procedures are shorter, omitting the need for a TC in the Pre-validation phase. The briefing  
270 document should contain a clear table of the changes compared to the previously reviewed  
271 development plan with justifications.

#### 272 **1.7. Example of procedural Timetable**

Date (example)	Step description
11 Dec	The Applicant sends the LOI to EMA
	Engagement with intended HTABS
05 Feb	The Applicant sends the briefing package to all parties
10 Feb	The Applicant sends the pre-validation TC presentation to all parties
13 Feb	Pre-validation TC all parties
28 Feb	The Applicant sends the revised briefing package to EMA administrative check
03 Mar	Start of the validated procedure (SAWP 1) Applicant sends Final briefing package to all parties
04 April	The SAWP secretariat circulates to the Applicant the List of Issues. This list can be shared by the Applicant to the HTABs (strongly recommended)

15 April	The Applicant sends the presentation and any requests responses for the F2F meeting considering the comments and clarifications received in the EMA List of Issues.
24 April	Pre-F2F TC together with the HTABs not including The Applicant
07 May	F2F meeting
15 May	The Applicant sends the minutes of the meeting to EMA and HTABs
23 May	EMA sends to the Applicant the final advice letter endorsed by the CHMP.
23 May	HTABs send comments on minutes/written responses depending on HTA practice

273

274 **2. Questions for public consultation on the Process for EMA-**  
275 **HTA Parallel Scientific Advice**

276 Please see the following link for questions for consultation.

277 Closing date for responses: **14<sup>th</sup> July 2014.**

278 <https://adobeformscentral.com/?f=WIJldoXFmz7BsTWjUwOIDA>

279 **(Software required to fill out form: - Any web browser on desktop, mobile, tablet)**

280

281 **3. Annex Briefing Document Template**

282 Rev. 0

283 **EMA -HTA <Parallel Scientific Advice/Protocol Assistance>**

284  
285 Briefing Document Template

286 *[Standard headings in the template should be used whenever possible; if it is*  
287 *considered necessary to deviate from the pre-specified headings to accommodate*  
288 *product-specific requirements, alternative or additional headings/sections may be*  
289 *considered.*

290 *This annotated template should be read in conjunction with the relevant guidelines*  
291 *that can be found on the website of the European Medicines Agency: 'EMA Guidance*  
292 *for Companies requesting Scientific Advice or Protocol Assistance' (EMA-H-4260-*  
293 *01-Rev.6).*

294 *Bracketing convention: {text}: Information that is required to be filled in; <text>:*  
295 *Text to be selected or deleted as appropriate.*

296 *[Text] is for explanation and guidance.*

297 *Formatting convention: Verdana 9 pt, single space, justified.*

298 *References convention:*

299 *- For citation of literature references, footnotes are preferred, alternatively the*  
300 *format (first author <et al.>, publication year) is recommended.]*

301 Invented Name: {}

302 Active substance: {}

303 Pharmaco-therapeutic group: {}

304 Intended indication(s): {}

305 Company: {}

306 Co-ordinators: {} *[to be completed at the time of final*  
307 *submission of the scientific advice/*  
308 *protocol assistance briefing document]*

309  
310 Agencies: {} *[list here all agencies providing advice]*

311 Version: {}

312 Date: {DD/MM/YYYY}

313

314	Table of Contents	
315		
316	List of Figures.....	12
317	List of Tables.....	12
318	List of Abbreviations.....	12
319	I. Summary .....	13
320	II. Product value proposition .....	13
321	III. Background information .....	13
322	IV. Questions and Company's positions .....	17
323	<A. EMA-only Questions .....	17
324	<B. EMA+HTA Questions .....	18
325	<C. HTA-only Questions .....	18
326	List of References .....	19
327	List of Annexes.....	20
328		

329 **List of Figures**

330 **List of Tables**

331 **List of Abbreviations**

332 *[Any acronyms or abbreviations used should also be defined the first time they*  
333 *appear in the text.]*

334

335 **I. Summary**

336 *[It is strongly recommended to address all elements outlined below (whenever*  
337 *applicable) for any advice request, regardless of the scope of the questions. This*  
338 *summary will inform the background information section of the final advice letter.*  
339 *An upper limit of 3 pages for the summary is recommended]*  
340

341 **Rationale for seeking advice**

342 *[Describe the scope of the questions and the rationale for the advice request (e.g.*  
343 *clinical/non-clinical/quality/significant benefit/similarity/conditional*  
344 *approval/exceptional circumstances).]*

345 **II. Product value proposition**

346 *[Describe value propositions and how the trial evidence will be used to support*  
347 *these]*

348 **III. Background information**

349 *[This section should give a comprehensive scientific overview of the product*  
350 *development program, providing relevant systematic information in sufficient detail,*  
351 *together with a critical discussion. However, it should be kept in mind that any*  
352 *information essential for the justification of a given question should also be*  
353 *sufficiently discussed in the corresponding Company's position. The proposed list of*  
354 *subsections is neither meant to be exhaustive nor mandatory, since the relevance or*  
355 *applicability of each subsection may vary depending on the scope of the advice*  
356 *request. In this respect, the potential direct or indirect relevance of the information*  
357 *covered in relation to the questions posed should be considered. Additional details*  
358 *can be included in study protocols, study reports, investigators' brochure provided*  
359 *as annexes. The use of tabulated overviews and graphs is encouraged.]*

360 **Disease to be treated**

361  
362 *[Outline main features of the disease and current standard therapy (referencing*  
363 *relevant guidelines and variations between the countries), referring to relevant*  
364 *publications as well as any current unmet need(s). For reimbursement decisions,*  
365 *the availability of treatment alternatives is a critical issue. Thus a solid discussion of*  
366 *treatment and treatment alternatives including national treatment guidelines and*  
367 *treatment algorithms is warranted]*

368 **Indication**

369 *[Specify the intended indication(s). Specify product positioning in the treatment*  
370 *pathway: (e.g. 1st line, 2nd line, 3rd line, screening pre-treatment, monitoring*  
371 *during treatment, etc.). Describe if it is a combination or monotherapy. Aim of*  
372 *treatment (preventive, curative, palliative, symptomatic, disease modifying). Target*  
373 *population]*  
374

375 **Description of the product**

376  
377 *[Include mode of action, chemical structure, pharmacological classification,*  
378 *proposed dosing regimen, route of administration and details of any additional*  
379 *diagnostic tests, medical devices or medical procedures that the use of the new*  
380 *product will incorporate.*

381 *Please specify the proposed wording for the intended indication, posology, and any*  
382 *special precautions or recommendations for use of the product (including a possible*  
383 *risk management strategy)]*

384 **Quality information on the product**

385 <Active substance>

386 <Finished product>

387 **Non-clinical information**

388 *[It is recommended to include a tabulated overview of all non-clinical studies*  
389 *(completed, ongoing and planned), including study number, main design features*  
390 *and GLP status. Main findings and safety margins may be described in the*  
391 *narrative.]*

392 <Pharmacology>

393 <Pharmacokinetics>

394 <Pharmacodynamics>

395 <Toxicology>

396

397 **Clinical information**

398 *[A tabular overview of all clinical studies (completed, ongoing and planned), should*  
399 *be included. Please try to include study number, protocol synopsis, location(s), trial*  
400 *objectives, trial design, randomisation, blinding, intervention, patient population,*  
401 *inclusion/exclusion criteria, identified subgroups, comparators, endpoints, HRQL,*  
402 *duration/follow-up and methods of analyses where applicable. Whilst the focus*  
403 *should be kept on the intended indication, the development in other indications*  
404 *could be briefly summarised, where relevant.]*

405 <Clinical pharmacology>

406 <Pharmacokinetics>

407 <Pharmacodynamics>

408 <Clinical efficacy>

409 *[A general overview of the clinical development program should be based on a*  
410 *comprehensive discussion of e.g. the main clinical results so far, dose-response,*  
411 *exploratory trials, special populations, supportive and pivotal clinical studies, and*  
412 *any analyses performed across trials (pooled and meta-analysis). The discussion*  
413 *should identify the most important findings and challenges in the clinical*  
414 *development program, and its compliance with legal requirements, relevant clinical*  
415 *guidelines, previous scientific advice (sufficiently justifying any deviations), etc.*

416 *Information on the geographical distribution of centres participating in the pivotal*  
417 *clinical studies can be reflected in this section.]*

418 <Clinical safety>

419 *[A general overview of the safety profile of the product should be based on a*  
420 *comprehensive discussion of e.g. patient exposure (safety database), adverse*  
421 *events observed so far, serious adverse events and deaths, laboratory findings,*  
422 *safety-related discontinuations, specific safety findings, immunological events,*  
423 *safety in special populations, etc.]*

424

425 <Quality development>

426 *[Relevance, and level of detail included may vary depending on the scope of the*  
427 *request. Special pharmaceutical aspects, if any, e.g. novel delivery system, etc.]*

428

429 <Non-clinical development>

430 *[Relevance, and level of detail included may vary depending on the scope of the*  
431 *request. Proof-of-concept and main toxicological findings could be informative.]*

432

433 Clinical development

434 *[Introduce and describe the status of the clinical development programme. A*  
435 *tabulated summary of completed, ongoing and planned clinical trials could be*  
436 *informative.*

437 *Include schematic(s) of the pivotal trial(s).*

438 *Include schematic of the development plan including the timing of MAA and the*  
439 *reimbursement application.*

440 *Briefly summarise the following aspects:*

441 *If scientific advice has been previously requested from the CHMP, national or non-*  
442 *EU (e.g. FDA)*

443 *Indicate if relevant CHMP guidance/CHMP advice has been followed or if any*  
444 *deviations have been made or proposed.*

445 *Indicate applicability and status of the Paediatric Investigation Plan (with or without*  
446 *deferral or waiver). Indicate availability and need for development in other special*  
447 *populations such as the elderly, male/female and ethnic minorities.]*

448

449 **Regulatory status**

450

451 *[Describe the worldwide regulatory status of the product (e.g. any existing MA, or*  
452 *planned MAA timelines), indicating planned type and timelines of marketing*  
453 *authorisation application (MAA) (e.g. full/mixed dossier; advanced therapy,*  
454 *biosimilar, generic/hybrid/ product) or variation.*

455 *If the product has received Orphan Drug Designation (ODD) related to the intended*  
456 *indication, state the orphan indication, the criteria on which the ODD was based*

457 *and, if applicable, the development plan to support similarity or clinical superiority.]*

458

459

460 **Economic evaluation plans**

461

462 *[This section is optional if no questions on economic evaluation are submitted.*

463 *If plans for the economic evaluation are provided, these should include to the extent*  
464 *possible:*

465 • *Description of the proposed model (diagram, modelling approach, time*  
466 *horizon, perspective)*

467 • *Data collection plans to inform the model:*

468 *o Evidence synthesis/meta-analysis – sources of evidence*

469 *o Comparators – MTC and indirect comparisons and evidence available*

470 *o Trial endpoints used to derive health outcomes in the model*

471 *o Quality of life – source and methods, tools used to measure QoL*

472 *o Incorporation of adverse effects*

473 *o Resource use – sources and methods, tools used to measure resource*  
474 *utilisation*

475 • *Methodological Approaches:*

476 *o Extrapolation – assumptions and data sources*

477 *o Continuation rules*

478 *o Use of surrogate outcomes*

479 *o Planned sensitivity analyses*

480 *Evidence gaps and model assumptions should be described.]*

481

482 **IV. Questions and Company's positions**

483 *[Questions should conform to the **scope** of the Scientific Advice/Protocol*  
484 *Assistance procedure (EMA-H-4260-01-Rev.6). It is recommended that questions*  
485 *are phrased in a way to allow for an unambiguous understanding of the question.*  
486 *The scope should be carefully considered in order to avoid too broad or too narrow*  
487 *questions.*

488 *The wording of the question should be clear and concise, avoiding extended*  
489 *reference to the justifications (which should be discussed in the Company position)*  
490 *and starting with e.g. "Does the CHMP agree that/with ...?".*

491 *Questions should be ordered in the corresponding section according to the expertise*  
492 *(also multidisciplinary) required for the assessment, and numbered sequentially.*

493 **IMPORTANT INFORMATION**

494 *Each question should be followed by a corresponding, separate Company's*  
495 *position including a comprehensive justification of the chosen approach.*

496 *All key information about the topic should be sufficiently discussed, so that*  
497 *the Company position can function as a 'stand-alone' argument. Issues to*  
498 *be covered could include the following: context and proposal, other options*  
499 *(potentially) considered together with a critical discussion on the relative*  
500 *merits and drawbacks of various approaches, possible consequences and*  
501 *eventual measures to ameliorate these. In general, an extension of 1 to 3*  
502 *pages for each Company position is recommended.*

503 *Cross-references to the relevant parts of the briefing document or annexes*  
504 *can be included if additional detail is needed to support the argument.]*

505 **<A. EMA-only Questions**

506 **Question 1**

507 {}

508

509 **Company's position**

510 {}

511

512 **Question 2**

513 {}

514

515 **Company's position**

516 {}

517 **<B. EMA & HTA Questions**

518

519 **Question {X}**

520 {}

521

522 **Company's position**

523 {}

524

525 **<C. HTA-only Questions**

526

527 **Question {X}**

528 {}

529

530 **Company's position**

531 {}

532

533 **List of References**

534 *[In general, any potentially relevant publications included in the list of references*  
535 *should be annexed (in .pdf format, either collated as a single document or if*  
536 *provided as single files, clearly identified and whenever possible compiled in one or*  
537 *more compressed files, for convenience). In case a relevant publication is not*  
538 *included at the time of validation, it should be ensured that it can be made available*  
539 *upon request.]*

540

541

542 **List of Annexes**

543 *[Annexes should be submitted as separate documents and should include any*  
544 *information potentially relevant to the questions, e.g.*

545 *Investigators' brochure*

546 *Study protocols (final, draft or outline/synopsis)*

547 *Study reports (final/draft/synopses)*

548 *Previous scientific advice received (e.g. CHMP Scientific advice/Protocol Assistance,*  
549 *any relevant official correspondence and meeting minutes with National Competent*  
550 *Authorities in EU-Member States, FDA and other non-EU Authorities)*

551 *Relevant guidelines (non-EMA)*

552 *Documents related to Orphan Drug Designation (e.g. COMP summary report)*

553 *Documents relating to Marketing Authorisation Application e.g. Day 120 List of*  
554 *Questions, Letter of undertaking.*

555 *Documents related to Paediatric Investigation Plans (e.g. PDCO summary report,*  
556 *opinion)*

557 *Contract/agreement consultant/CRO - sponsor*

558 *Literature references]*