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4 **Guideline on the scientific application and the practical**  
5 **arrangements necessary to implement Commission**  
6 **Regulation (EC) No 507/2006 on the conditional**  
7 **marketing authorisation for medicinal products for human**  
8 **use falling within the scope of Regulation (EC) No**  
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This guideline draft has been updated in order to reflect the experience accumulated with Conditional Marketing authorisations and is therefore released for repeated public consultation.

Comments should be provided using this [template](#). The completed comments form should be sent to [CMA\\_guideline@ema.europa.eu](mailto:CMA_guideline@ema.europa.eu).

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19 726/2004

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## 43 **Executive summary**

44 This guideline has been developed in order to provide advice on the scientific application and the  
45 practical arrangements necessary to implement the legal provisions on the conditional marketing  
46 authorisation.

## 47 **1. Introduction (background)**

48 According to Article 14(7) of Regulation (EC) No 726/2004, following consultation with the applicant,  
49 an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the  
50 Agency. The list of these obligations shall be made publicly accessible. By way of derogation, such  
51 authorisation shall be valid for one year, on a renewable basis.

52 This provision for a conditional marketing authorisation is further defined in Regulation (EC) No.  
53 507/2006.

54 Conditional marketing authorisation, in line with the defined scope and criteria and in the interest of  
55 public health, is usually appropriate for products where benefit-risk balance is such that the immediate  
56 availability outweighs the limitations of less comprehensive data than normally required, i.e. medicines  
57 with an established potential to address an unmet medical need.

## 58 **2. Scope**

59 This guideline addresses granting and renewing a conditional marketing authorization, as well as  
60 granting of a marketing authorisation not subject to specific obligations following their completion. This  
61 guideline should be followed unless otherwise justified.

## 62 **3. Legal basis**

63 The legal basis for this guideline is Article 11 of Commission Regulation (EC) No. 507/2006 on the  
64 conditional marketing authorisation for medicinal products for human use falling within the scope of  
65 Regulation (EC) No 726/2004.

## 66 **4. Granting of a conditional marketing authorisation**

### 67 ***4.1. Applicant's request for a conditional marketing authorisation***

68 A conditional marketing authorisation may be requested by the applicant or proposed by the CHMP.  
69 The applicant is invited to notify the EMA about its intention to request a conditional marketing  
70 authorisation as part of the "letter of intent" to be sent to the EMA in advance of the marketing  
71 authorisation application submission.

72 The applicant may present a request for a conditional marketing authorisation at the time of the  
73 application for marketing authorisation. A request for conditional marketing authorisation shall be  
74 submitted in module 1.5.5 of the EU-CTD.

75 The request should consist of justifications to show that the medicinal product falls within the scope of  
76 the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional  
77 marketing authorisation are fulfilled (Article 4), together with the applicant's proposal for completion of  
78 ongoing or new studies and, if applicable, also specific proposals for collection of pharmacovigilance  
79 data. The request may cross-refer to specific parts of the application.

80 Upon receipt of a valid application containing a request for conditional marketing authorisation, the  
81 EMA will inform the Commission.

#### 82 **4.1.1. Justification that the medicinal product falls within the scope of the** 83 **conditional marketing authorisation**

84 The applicant should justify that the medicinal product falls within the scope of the conditional  
85 marketing authorisation regulation. The categories of medicinal products that fall within the scope of  
86 the conditional marketing authorisation regulation are defined in Article 2 of Commission Regulation  
87 (EC) No 507/2006. These are products for human use falling under Article 3(1) and (2) of Regulation  
88 (EC) No 726/2004, and belonging to at least one of the following categories:

89 1. Seriously debilitating diseases or life-threatening diseases

90 The severity of the disease, i.e., its seriously debilitating, or life-threatening nature needs to be  
91 justified, based on objective and quantifiable medical or epidemiologic information. Whereas a  
92 life-threatening disease is relatively easy to describe based on figures of mortality and life  
93 expectancy, justifying that a disease is seriously debilitating will have to consider morbidity and  
94 its consequences on patients' day-to-day functioning. For a disease to be considered seriously  
95 debilitating it would need to have a well-established major impact on patients' day-to-day  
96 functioning either already early in the course of the disease, or in the later stages. These  
97 aspects should be quantified in objective terms, as far as possible. Furthermore, serious  
98 debilitation, or fatal outcome should be a prominent feature of the target disease and  
99 therapeutic indication, i.e. affect an important portion of the target population.

100 2. Medicinal products to be used in emergency situations

101 A justification should be provided that the medicinal product is intended for use in emergency  
102 situations, in response to public health threats duly recognised either by the WHO or by the  
103 Community (Decision No. 2119/98/EC). A reference to the relevant WHO Resolution or  
104 Decision, or to the measures adopted by the Commission in the framework of Council and  
105 Parliament Decision No. 2119/98/EC should be provided.

106 3. Orphan medicinal products

107 For requests submitted in accordance with article 2 (3) of Commission Regulation (EC) No.  
108 507/2006, a copy of the Commission Decision on the designation as an orphan medicinal  
109 product should be provided.

#### 110 **4.1.2. Fulfilment of the requirements for conditional marketing** 111 **authorisation**

112 The requirements for a conditional marketing authorisation Regulation are described in Article 4 of  
113 Commission Regulation (EC) No. 507/2006. In its request for a conditional marketing authorisation,  
114 the applicant should justify why in their opinion each of these requirements are expected to be met:

115 **(a) The risk-benefit balance of the product is positive**

116 Article 4 (a) of Commission Regulation (EC) No. 507/2006 states that one of the criteria for granting of  
117 a conditional marketing authorisation is that the risk-benefit balance of the medicinal product is  
118 positive, as defined in Article 1(28a) of Directive 2001/83/EC.

119 The demonstration of a positive benefit-risk balance should be based on scientific evidence, in  
120 particular evidence from clinical trials. The available evidence should be sufficient to demonstrate the

121 benefits of the product to a degree that allows them to be assessed against the risks identified in the  
122 studies conducted and the risks related to the absence of some of the data (see also requirement (d)  
123 below).

124 Products to be used in emergency situation, in response to recognised health threats, may provide  
125 particularly important benefits, therefore higher risks related to the absence of some data may be  
126 acceptable. Article 4(1) states that in such cases a conditional marketing authorisation can be granted  
127 also if preclinical or pharmaceutical data are not comprehensive. Such applications will be assessed on  
128 a case-by-case basis, taking into account the respective health threats and effects of the product. For  
129 other categories within the scope of Article 2 only the clinical data can be less comprehensive than is  
130 normally the case.

131 The elements of the comprehensive data that are not available at the time of authorisation should be  
132 discussed by the applicant and their acceptability justified based on the strength of available results  
133 and taking into account the requirement for a positive benefit-risk balance. If justified, such elements  
134 could include:

- 135 • results on longer-term, clinically most relevant efficacy endpoint (having used an intermediate  
136 endpoint at time of authorisation), e.g. overall survival vs. progression-free survival,
- 137 • safety and efficacy results from a larger database or for longer duration, with the same  
138 endpoint(s) and in same population, e.g. response rate at a later time cut-off,
- 139 • further data on additional endpoints / specific issues identified, e.g. effects on metastases,  
140 hepatic disorders,
- 141 • further data in important sub-populations, e.g. patients with resistance or a particular  
142 biomarker that may be important,
- 143 • further data on impact of other medication, e.g., efficacy data with other co-medication for  
144 combination therapies.

145 The establishment of beneficial effects at the time of authorisation could potentially be based on  
146 intermediate endpoints that are reasonably likely to translate into clinical benefit, but do not directly  
147 measure the clinical benefit. If such approach is proposed, the suitability of the intermediate endpoint  
148 should be discussed, and its ability to establish or predict the clinical benefit justified based on the  
149 available evidence. In particular, the applicant should discuss the level of certainty with which the  
150 intermediate endpoint predicts clinical benefit, and why any remaining uncertainties would be  
151 acceptable. Conditional marketing authorisation could be appropriate when an intermediate endpoint  
152 shows benefits that outweigh any uncertainties about the extent of the clinical benefit it translates to,  
153 and when confirmation on the clinical benefits is still required. It has to be also clarified that in cases  
154 when the used intermediate endpoint is a fully validated surrogate endpoint and further data on actual  
155 clinical benefits are not required, a marketing authorisation not subject to specific obligations might be  
156 appropriate.

157 Scenarios of establishing a positive benefit-risk balance with less than comprehensive data include also  
158 situations when comprehensive data would require other additional data (e.g. with longer duration or  
159 more data on particular subgroups), but the benefits demonstrated with the available data outweigh  
160 the risks and it would be disproportionate from the public health perspective to delay the approval of  
161 the product.

162 The limitations in the extent of safety data available contribute to the uncertainties and are to be taken  
163 into account in the benefit-risk balance. The acceptability of safety of the product has to be assessed

164 on a case by case basis, based on the safety data available and taking into account the demonstrated  
165 benefits of the product.

166 In summary, for a conditional marketing authorisation it might be acceptable that studies are smaller  
167 in size and/or with a shorter duration and/or different endpoints than normally expected for  
168 confirmatory studies in the particular indication for respective type of the product. However, it has to  
169 be substantiated that the benefits demonstrated with the available data outweigh the risks, also  
170 considering the increased uncertainties around the benefits and risks that are related to the less  
171 comprehensive nature of the data. Since the risks related to limitations of data are unlikely to be  
172 estimated precisely, it is expected that beneficial effects observed are particularly strong for the  
173 respective endpoint in the light of the totality of evidence available, therefore indicating a particularly  
174 promising product.

175 To address the requirement of article 4 (1) (a), the applicant will have to provide a justification  
176 outlining the following points:

- 177 • Positive risk-benefit balance of the product.
- 178 • A discussion of any aspects of the positive benefit risk balance that require confirmation from  
179 further studies (e.g., confirmation of effect on other endpoints, long-term effects, effect in  
180 special populations or identification of responders).

181 **(b) It is likely that the applicant will be able to provide comprehensive data**

182 By way of specific obligations the holder of a conditional marketing authorisation shall be required to  
183 complete ongoing studies or to conduct new studies, with a view to providing comprehensive clinical  
184 data and confirming that the risk-benefit balance is positive. In emergency situations, specific  
185 obligations to provide comprehensive non-clinical or pharmaceutical data may also be required.

186 Comprehensive data are intended to confirm that the benefit risk balance is positive, for instance, by  
187 checking the coherence of the available data on primary or secondary endpoints in more mature data  
188 sets or in additional studies in related indications, providing information on clinically most relevant  
189 (long term) endpoints, investigating the effect duration, providing larger safety database, and  
190 generally providing a better understanding of the efficacy and safety of the product.

191 Specific obligations should aim to obtain evidence that has a consequence on confirming the benefit-  
192 risk in the approved indication and to achieve a comprehensive dossier on the product. There should  
193 be a clear explanation and rationale on what are the remaining questions relating to the safety and  
194 efficacy in the proposed indication, and how fulfilment of the obligation will result in a resolution of  
195 these questions.

196 It is important that the development should be completed as soon as possible to ensure that any  
197 uncertainties due to the lack of comprehensive data do not persist indefinitely.

198 The applicant should explain how comprehensive data can be provided within an agreed timeframe.  
199 The applicant should provide reassurance as to the feasibility and quality of studies to be performed as  
200 specific obligations. Granting of a marketing authorisation may for instance lead to potential difficulties  
201 in recruitment, breaking of blinding in ongoing or future studies, or otherwise compromise the  
202 statistical analyses, particularly for trials with patients from the same population as covered by the  
203 authorisation.

204 Safety may need intense monitoring to allow an informed judgement on the positive benefit risk  
205 balance at the time of the annual renewal. Specific obligations may be imposed also in relation to the  
206 collection of pharmacovigilance data.

207 The CHMP will assess the claims of the applicant about the feasibility and appropriateness of granting a  
208 conditional marketing authorisation. Where (timely) completion of further studies required for the  
209 confirmation of a positive benefit risk balance cannot be expected, this may lead to a negative opinion  
210 on the granting of a conditional marketing authorisation.

211 The applicant is strongly encouraged to discuss in advance of the submission of marketing  
212 authorisation application (e.g. in a scientific advice procedure) the overall development plan and  
213 design of studies that are planned to be completed before authorisation and conducted as specific  
214 obligations following the granting of a conditional marketing authorisation. When discussing  
215 development programme for a conditional marketing authorisation it is recommended to include  
216 prospective scenario building for the potential marketing authorisation, planning the impact of future  
217 outcomes on next steps in the development programme (including on proposed specific obligations).

218 The applicant for an orphan medicinal product for which the designation is based on significant benefit  
219 over existing therapies, when preparing and discussing the development programme, is encouraged to  
220 consider also suitability of the data to be generated for confirmation of the orphan designation at the  
221 time of marketing authorisation.

222 For each ongoing or new study that is proposed to be provided as part of a specific obligation, a short  
223 description should be provided:

- 224 • Study synopsis. The structure and content of the synopsis will vary depending on the type of  
225 study and type of specific obligation. For a typical clinical efficacy study, the information  
226 provided should include:
  - 227 ○ Title
  - 228 ○ Introduction (rationale)
  - 229 ○ Treatments (specific drugs, doses and procedures)
  - 230 ○ Patient population and the number of patients to be included
  - 231 ○ Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded  
232 evaluators and unblinded patients and/or investigators)
  - 233 ○ Kind of control(s) (e.g., placebo, no treatment, active drug, dose-response) and study  
234 configuration (parallel, cross-over)
  - 235 ○ Method of assignment to treatment (randomization, stratification)
  - 236 ○ Sequence and duration of all study periods, including pre-randomisation and post-  
237 treatment periods, therapy withdrawal periods and single- and double blind treatment  
238 periods.
  - 239 ○ Primary and secondary efficacy and safety variables
  - 240 ○ Description of main methods for interim and final analyses of efficacy or safety.
  - 241 ○ Timing and description of important milestones for the study start, conduct, analysis,  
242 and reporting (including contents of interim reports).
  - 243 ○ A critical discussion about the rationale and feasibility of the study

#### 244 **(c) Fulfilment of unmet medical need**

245 Article 4 paragraph 1(c) of Commission Regulation (EC) No. 507/2006 states that one of the  
246 requirements for granting of a conditional marketing authorisation is that unmet medical needs will be

247 fulfilled. Paragraph 2 specifies that unmet medical needs mean a condition for which there exists no  
248 satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method  
249 exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to  
250 those affected.

251 Fulfilment of an unmet medical need is a major feature of products suitable for conditional marketing  
252 authorisation and indicates the particular value that the product is expected to bring, which also allows  
253 outweighing not just the risks clearly identified at the time of authorisation, but also the risks related  
254 to less comprehensive data than would be normally the case.

255 To address this requirement, applicants should justify that there exists an unmet medical need and  
256 that it is necessary to introduce new methods when no methods exist, or that it is necessary to provide  
257 a major improvement on the existing methods. The demonstration of fulfilment of an unmet medical  
258 need has to be justified on a case-by-case basis. The justifications should quantify the unmet medical  
259 need based on medical or epidemiologic data.

260 In general, major therapeutic advantage would normally be based on meaningful improvement of  
261 efficacy or clinical safety, such as having an impact on the onset and duration of the condition, or  
262 improving the morbidity or mortality of the disease. In exceptional cases, also major improvements to  
263 patient care could provide a major therapeutic advantage, e.g. if the new treatment is expected to  
264 address serious existing issues with treatment compliance or if the treatment allows ambulatory  
265 treatment instead of treatment in hospital only.

266 The advantages should be demonstrated over existing methods used in clinical practice (if any), using  
267 robust evidence, normally from well conducted randomised controlled trials (evidence-based  
268 demonstration of benefit).

269 As advantages over existing treatments are relevant also for confirmation of orphan designation by the  
270 Committee for Orphan Medicinal Products (COMP) for products where the designation is based on  
271 significant benefit, the CHMP and COMP will cooperate in their assessments of such applications as  
272 necessary (e.g. by sharing the CHMP assessment reports with COMP).

273 In order to support the claim that unmet medical needs will be fulfilled, the applicant is expected to  
274 provide:

- 275 • A critical review of available methods of prevention, medical diagnosis or treatment,  
276 highlighting an unmet medical need
- 277 • Quantification of the unmet medical need taking into account technical argumentation (e.g.,  
278 quantifiable medical or epidemiologic data)
- 279 • A justification of the extent to which the medicinal product will address the unmet medical  
280 need

281 **(d) The benefits to public health of the immediate availability outweigh the risks inherent in**  
282 **the fact that additional data are still required**

283 The applicant will have to provide a justification to substantiate the claim that the benefits to public  
284 health of the immediate availability of the medicinal product outweigh the risks inherent in the fact  
285 that additional data are still required. The justification should assess the impact of *immediate*  
286 availability on public health, based as far as possible on objective and quantifiable epidemiological  
287 information, as opposed to availability when comprehensive clinical data are expected to be available.  
288 Similarly, the risks inherent in the fact that additional data are still required shall be quantified as far  
289 as possible on objective and quantifiable terms (see also requirement (a) above).



290 In order to support the claim that the benefits to public health outweigh the risks inherent in the fact  
291 that additional data are still required, the applicant will have to provide a justification addressing the  
292 following points:

- 293 • Benefits to public health of the immediate availability on the market
- 294 • Risks inherent in the fact that additional data are still required
- 295 • How the benefits to public health in the context of immediate availability outweigh the risks  
296 (also taking into account the remaining questions)

#### 297 **4.2. Agency advice prior to submission of a request for conditional** 298 **marketing authorisation**

299 Article 10 of Commission Regulation (EC) No. 507/2006 addresses advice prior to submission of a  
300 marketing authorisation application. Applicants for a potential conditional marketing authorisation may  
301 request CHMP scientific advice or protocol assistance, as applicable, on whether a specific medicinal  
302 product being developed for a specific therapeutic indication falls within one of the categories set out in  
303 Article 2 and fulfils the requirement laid down in Article 4(1)(c) (“unmet medical needs will be  
304 fulfilled”). Please see also section 1.2.(b) above regarding the scientific advice on development  
305 programme for products intended for conditional marketing authorisation and the recommended  
306 approach of prospective scenario building. Applicants may also consider requesting parallel scientific  
307 advice with Health Technology Assessment bodies.

308 In addition, the intention to request a conditional marketing authorisation and any practical or  
309 procedural issues with regard to a potential request for conditional marketing authorisation should be  
310 addressed at pre-submission meetings with the EMA and rapporteurs.

311 The applicants are reminded that prospective planning of conditional authorisations is important for  
312 ensuring swift assessment procedure, and is especially important in cases when accelerated  
313 assessment is requested.

#### 314 **4.3. CHMP proposal for a conditional marketing authorisation**

315 During the scientific assessment, after having consulted with the applicant, the CHMP may also  
316 propose a conditional marketing authorisation. During the consultation, the applicant will be requested  
317 to provide their position on the possible granting of a conditional marketing authorisation and, in case  
318 of an agreement also their justification regarding fulfilment of the requirements for conditional  
319 marketing authorisation set out in Article 4 of Commission Regulation (EC) No. 507/2006. To ensure  
320 consistency of application the response should address the elements set out in section 1.2.

321 The proposal should be made as early as possible, in order to allow sufficient time for agreement on  
322 the details of the specific obligations. Normally, the proposal will be made to the applicant in the day  
323 120 list of questions, or exceptionally later, in the day 150 joint assessment report and day 180 list of  
324 outstanding issues. The applicant may be asked to provide any relevant additional information to  
325 substantiate the fulfilment of the requirements for conditional marketing authorisation, as necessary.  
326 The reasons for proposing a conditional marketing authorisation will be detailed in the CHMP  
327 assessment report.

#### 328 **4.4. CHMP assessment of a request for conditional marketing authorisation**

329 The acceptability of the applicant’s request for a conditional marketing authorisation will be part of the  
330 scientific review. The CHMP shall summarise its assessment of the request for conditional marketing

331 authorisation, and particularly the claims that the medicinal product falls within the scope of the  
332 regulation for conditional marketing authorisation and that the requirements of Article 4 have been  
333 met. The assessment will be reflected in the relevant assessment reports and in the final CHMP  
334 assessment report. Similarly, in case of CHMP proposal for a conditional marketing authorisation after  
335 having consulted with the applicant, the CHMP will assess if the medicinal product falls into the scope  
336 of the regulation for conditional marketing authorisation and if the requirements of Article 4 have been  
337 met. The assessment will be reflected in the relevant assessment reports and in the final CHMP  
338 assessment report.

339 In case the CHMP is of the opinion that any of the requirements for the granting of a conditional  
340 marketing authorisation are not fulfilled, and where the requirements for granting of a marketing  
341 authorisation not subject to specific obligations are also not met, this would lead to the adoption of a  
342 negative opinion on the granting of a marketing authorisation.

343 Upon granting of a conditional marketing authorisation, the specific obligations and the timeframe for  
344 their completion will be clearly specified in the conditional marketing authorisation (Annex II to the  
345 Commission Decision), and will be made publicly available by the Agency as part of the European  
346 Public Assessment Report.

#### 347 ***4.5. Information included in the summary of product characteristics and*** 348 ***package leaflet***

349 Enhanced transparency regarding the assessment of such applications and clear information should be  
350 provided to patients and healthcare professionals on the conditional nature of the authorisations.

351 The summary of product characteristics and package leaflet will mention that a conditional marketing  
352 authorisation has been granted subject to certain specific obligations to be reviewed annually (see  
353 Guideline on summary of product characteristics and Quality Review of Documents product information  
354 templates).

#### 355 ***4.6. Periodic safety update reports***

356 Article 9 of Commission Regulation No. 507/2006 states that the periodic safety update reports shall  
357 be submitted to the Agency and Member States immediately upon request or at least every six months  
358 following the granting or renewal of a conditional marketing authorisation. The requirements for PSUR  
359 submission will be reflected in the EURD list and referred to in Annex II to the marketing authorisation.

## 360 **5. Renewal of a conditional marketing authorisation**

361 Based on Article 14 (7) of Regulation (EC) 726/2004 a conditional marketing authorisation is valid for  
362 one year. Thereafter, following Article 6 (1) of Commission Regulation 507/2006, the conditional  
363 marketing authorisation may be renewed annually.

364 Following Article 6 (2) of Commission Regulation 507/2006, the marketing authorisation holder shall  
365 apply for its renewal at least six months before its expiry and shall provide the Agency with an interim  
366 report on the fulfilment of the specific obligations to which it is subject.

367 The CHMP will assess the renewal application on the basis of the risk-benefit balance and formulate an  
368 opinion whether the specific obligations or their timeframes need to be retained or modified and  
369 whether the marketing authorisation should be maintained, varied, suspended or revoked.

370 The marketing authorisation holders are reminded that specific obligations are imposed with an aim to  
371 confirm that the benefit-risk balance is positive, therefore in case of a non-compliance with specific

372 obligations the CHMP may consider that the positive benefit-risk balance is not confirmed and  
373 recommend appropriate regulatory action.

374 In order to ensure that medicinal products are not removed from the market except for reasons related  
375 to public health, based on Article 6 (4) of Regulation (EC) 507/2006 the conditional marketing  
376 authorisation will remain valid until the European Commission adopts a decision following the renewal  
377 assessment procedure, provided that the renewal application has been submitted on time.

378 The renewal of the marketing authorisation will continue to be conducted annually, while the  
379 authorisation remains conditional. When the specific obligations will be completed and a marketing  
380 authorisation not subject to specific obligations issued (as defined in Article 7 of Regulation (EC)  
381 507/2006), it will be valid for 5 years.

## 382 **5.1. Documents to be submitted**

### 383 **5.1.1. General requirements**

384 In order to allow the CHMP to confirm the risk-benefit balance of the medicinal product and to review  
385 the specific obligations and their timeframes for completion, the marketing authorisation holder should  
386 provide at least the following information in their renewal application<sup>1</sup>:

- 387 a. A chronological list of specific obligations and other conditions to the MA submitted since  
388 grant of marketing authorisation indicating scope, status, date of submission and date  
389 when issue has been resolved (where applicable).
- 390 b. Summary of product characteristics, Annex II, labelling and package leaflet
- 391 c. An interim report on the fulfilment of the specific obligations, including details for each  
392 specific obligation. The aim of this report is to inform about the status of the data that is  
393 the subject of a specific obligation, to provide interim data as appropriate and agreed, and  
394 to inform about the likelihood that the applicant will be able to provide the data (see also  
395 section 3.2).
- 396 d. A clinical expert statement addressing the current benefit-risk of the product on the basis  
397 of data generated in Specific Obligations and taking into account any other safety  
398 (including PSUR) or efficacy data accumulated since the granting of the marketing  
399 authorisation. In exceptional cases, a non-clinical or quality expert statement may also be  
400 required.
- 401 e. Data related to specific obligations, where the due date for submission of such data  
402 coincides with the renewal application.

403 If the data included in the renewal submission warrants an update of the product information or risk  
404 management plan, such proposed changes can be included as part of the renewal procedure.

405 Data included in other submissions, but relevant to the benefit-risk balance of the product should be  
406 taken into account in preparation of the renewal application. However, the renewal should not replace  
407 other required submissions (e.g. variations) and submission of such data should not be postponed to  
408 the next renewal.

409 Practical details on the presentation and submission of renewal applications are given in the EMA post-  
410 authorisation guidance document on the EMA website.

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<sup>1</sup> These requirements apply to annual renewal of conditional marketing authorisations only, which are outside the scope of  
"Guideline on the processing of renewals in the centralised procedure" EMEA/CHMP/2990/00

## 411 **5.1.2. Requirements for the interim report on the specific obligations**

412 One report should be submitted for the product including all specific obligations. The structure and  
413 contents of the interim report will vary depending on the type of study, and available data. The  
414 purpose of the information to be submitted for each study is to allow an assessment of the impact of  
415 available data on benefit-risk balance, assessment of the fulfilment of the specific obligations, and  
416 should provide sufficient information to allow an assessment of whether such obligations and their  
417 timeframes should be retained or modified. In the typical situation where the specific obligations refer  
418 to data collected from clinical trials, the following general structure is suggested for interim reports. It  
419 is understood that even for clinical studies, depending e.g., on the design and blinding of trial, one or  
420 more subheadings may not be applicable and other data may be required. Agreement on the key  
421 elements of these reports on fulfilment of specific obligations should be sought during the assessment  
422 procedure.

423 Within the interim report for a product, for each specific obligation consisting of a clinical study, it is  
424 recommended to provide the following items:

425 a. Title page and synopsis

426 For each of the ongoing or new studies that is part of a specific obligation, a short description  
427 (limited to one page or less) should be provided. The description should address the expected  
428 overall study plan and design.

429 b. Introduction

430 Describe the status of development of the study, any issues that are still outstanding or that  
431 have a significant impact on the feasibility of the study, expected delays, etc.

432 c. Accrual

433 Describe enrolment, accrual over time, accrual by centre, country, and region, accrual by  
434 treatment group, information on data availability and follow-up status, and duration of follow-  
435 up. Include analyses of issues such as assumptions about accrual, event rates, implications for  
436 study power, evaluation of changes in characteristics of enrolled patients over time; conditional  
437 power calculations, implications for timing of final analysis.

438 d. Baseline Characteristics

439 Display baseline variables by treatment group, eligibility. Describe any issues with screening  
440 criteria, impact of exclusion criteria, and issues of generalisability.

441 e. Adverse Events

442 Describe adverse events by treatment and severity, at the body system level and at the level  
443 of preferred term, and describe the occurrence of serious adverse events.

444 f. Study Endpoint Analysis

445 Describe the expected timing and, to the extent that this can be published based on the  
446 protocol and operating procedures, the outcome, of interim analyses or of final analyses, or  
447 other available data, as appropriate.

448 g. Study conduct and compliance

449 Describe treatment compliance, compliance with efficacy and safety assessments, significant  
450 changes in the conduct of the study or planned analyses, important protocol deviations,  
451 dropout and missing data, critical quality assurance and quality control findings.

452 Final reporting of clinical trials should follow the conventional format of study reports (see ICH Topic E3  
453 Note for guidance on structure and content of clinical study reports, CPMP/ICH/137/95).

## 454 **6. Marketing authorisation not subject to specific obligations**

455 At any time, when the specific obligations have been fulfilled, the CHMP may adopt an opinion  
456 pursuant to Article 7 of Regulation (EC) No 507/2006 recommending granting of a marketing  
457 authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing  
458 authorisation not subject to specific obligations'). This can be done at the time of renewal of the  
459 conditional marketing authorisation or at the time of assessment of the data submitted to fulfil the last  
460 remaining specific obligation. Where the submission of the results of specific obligations leads to the  
461 need to update product information, this will be included in the same Article 7 opinion.

462 When submitting the last specific obligation data and in view of a possible change to a 'marketing  
463 authorisation not subject to specific obligations', the marketing authorisation holder should address  
464 this in their submission and provide updated product information and a clinical expert statement in  
465 support of the possible granting of a 'marketing authorisation not subject to specific obligations'.

466 The reasons for proposing the granting of a 'marketing authorisation not subject to specific obligations'  
467 will be detailed in the CHMP assessment report.

## 468 **Abbreviations**

469	CAT	Committee for Advanced Therapies
470	CHMP	Committee for Medicinal Products for Human Use
471	COMP	Committee for Orphan Medicinal Products
472	CTD	Common Technical Document (an agreed format for documentation)
473	EMA	European Medicines Agency
474	EURD list	List of EU reference dates and frequency of submission of PSURs
475	PDCO	Paediatric Committee
476	PRAC	Pharmacovigilance Risk Assessment Committee
477	PSUR	Periodic Safety Update Report
478	WHO	World Health Organisation

## 479 **References**

- 480 1. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004  
481 laying down Community procedures for the authorisation and supervision of medicinal products for  
482 human and veterinary use and establishing a European Medicines Agency, as amended
- 483 2. Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing  
484 authorisation for medicinal products for human use falling within the scope of Regulation (EC) No  
485 726/2004 of the European Parliament and of the Council