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HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products — authorisations, EMA

COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR PAEDIATRIC INVESTIGATION PLANS

(ARTICLE 10 OF REGULATION (EC) NO 1901/2006)

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Deadline for public consultation: 18 December 2013

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary draft. The suggestions contained in this document do not prejudice the form and content of any future proposal made by the Commission.

Contact:

Responses should be sent preferably by email to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels.

The subject of the letter/email should refer to 'PCPIP/13/01 — Public consultation on PIP guideline'.

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I. ABOUT THE CONSULTATION

A. INTRODUCTION

In accordance with Article 10 of the Paediatric Regulation (Regulation (EC) No 1901/2006), in consultation with the Member States, the Agency and other interested parties, the Commission has to draw up detailed arrangements concerning the format and content which applications for agreement on or modification of a paediatric investigation plan and requests for waivers or deferrals must follow in order to be considered valid and concerning the operation of the compliance check.

In September 2008 the Commission published the relevant guideline¹. It has been in use for the last five years. In its recent report on the Paediatric Regulation², the Commission undertook to review the guideline in order to take into account the experience gained, including the considerable number of requests to modify paediatric investigation plans.

The Commission therefore requested the European Medicines Agency and its Paediatric Committee to suggest amendments to the current guideline which they considered appropriate. This document is based on but not identical to those suggestions, for which the Commission is grateful. At the same time this means, however, that the present document does not necessarily represent the Commission's position on all the issues. Instead, it is a tool to explore the views of interested parties on a preliminary proposal.

In discussing suggestions for a revised version of the guideline, the Agency took the following approach:

- The Agency considered that the guideline could benefit from some improvement and adaptation to current implementation, but that its general structure and content did not require substantial changes.
- It deleted unnecessary or repetitive details, and simplified the language and style used where possible.
- It added new concepts: definitions of key elements and extrapolation, and the request for an 'Application Summary' to be attached to the application's scientific documents (parts B-E).
- It updated other definitions, such as that of condition.
- It clarified the difference between condition and indication and the respective roles.
- It mentioned explicitly rather than implicitly the possibility of having multiple paediatric investigation plans for the same product.

The purpose of this concept paper is to support the Commission in further exploring which parts of the current guideline should be updated. For the sake of clarity changes are, however, not tracked in the document.

¹ Communication from the Commission — Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals, OJ C 243, 24.9.2008, p. 1.

² Better medicines for children — From concept to reality, COM(2013) 443 final.

The concept paper is now being put out for public consultation. Replies or comments should be submitted by 18 December 2013 at the latest.

B. CONSULTATION TOPICS

The consultation text is supplemented by a number of specific consultation items in boxed text raising questions on which the Commission seeks input from interested parties.

Respondents are invited to address those points specifically. Comments on any other part or aspect are also welcome.

C. HOW CAN I CONTRIBUTE?

Stakeholders are invited to comment on this concept paper, and on the boxed text in particular, by 18 December 2013 at the latest. Responses should be sent (preferably by email) to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels. The subject line of the letter or email should refer to 'PCPIP/13/01 — Public consultation on PIP guideline'.

When you submit your comments and responses, please state your affiliation or whether you submit your comments as a private individual. If you represent an association, please indicate clearly what type of association it is (patients, health professionals, manufacturers, marketing authorisation holders, etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

An acknowledgement of receipt will be issued for each contribution received.

The contributions received and the identity of the contributors will be made publicly available on the 'Public health' website³, unless the contributor objects to the publication of his or her personal data on the grounds that it would harm his or her legitimate interests. In that case the contribution may be published in anonymous form. Otherwise the contribution will not be published, nor will its content normally be taken into account. For more information on the processing of your personal data in the context of this consultation, you should read the specific Privacy Statement available on the Public health website.

Professional organisations are invited to register in the EU's Register of Interest Representatives (http://europa.eu/transparency-register/index_en.htm) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structure of interest representatives.

D. WHAT WILL HAPPEN NEXT?

All contributions will be carefully analysed. Any subsequent Commission proposal will build on the consultation.

³ http://ec.europa.eu/health/human-use/index_en.htm.

1 II. THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

2 1. INTRODUCTION

3 In accordance with Article 10 of Regulation (EC) No 1901/2006 of the European Parliament
4 and of the Council on medicinal products for paediatric use⁴ (hereinafter ‘the Paediatric
5 Regulation’), this guideline sets out the detailed arrangements concerning the format and
6 content of applications for agreement on or modification of a paediatric investigation plan and
7 requests for waivers and deferrals. The guideline also lays down the arrangements for the
8 operation of the compliance check referred to in Article 23 and Article 28(3) of the Paediatric
9 Regulation. Finally, pursuant to Article 45(4) of the Paediatric Regulation, the guideline spells
10 out the criteria for assessing the significance of studies started before and completed after the
11 entry into force of the Paediatric Regulation. This guideline replaces the previous version
12 from 2008⁵.

13 For the purpose of this guideline the following definitions should apply:

- 14 (a) condition: any deviation from the normal structure or function of the body, as
15 manifested by a characteristic set of signs and symptoms, typically a recognised
16 distinct disease or a syndrome; a condition may also be represented by a specific use
17 during specialised therapeutic or diagnostic procedures (e.g. use in bone marrow
18 transplantation, contraception). As the medicines development is different, diagnosis,
19 prevention and treatment of a condition will be considered as separate;
- 20 (b) paediatric investigation plan indication: proposed indication in the paediatric
21 population for the purpose of a paediatric investigation plan, and at the time of
22 submission of the paediatric investigation plan, within a specific condition;
- 23 (c) proposed indication: the indication for use in adults (and/or in specified paediatric
24 subsets), as submitted by an applicant. In case of a completed or ongoing adult
25 development, this is the starting point to identify the condition for potential
26 paediatric use;
- 27 (d) measures: any studies, trials, data and pharmaceutical form and formulation
28 development proposed to generate new scientific information, with a view to
29 ensuring that in accordance with Article 15(2) of the Paediatric Regulation the
30 necessary data are generated determining the conditions in which a medicinal
31 product may be authorised to treat the paediatric population;
- 32 (e) key elements: each measure in a paediatric investigation plan may contain one or
33 more specific key elements, as specified in the annex to this guideline;
- 34 (f) extrapolation: extending information and conclusions available from studies in one
35 or more subgroups of the patient population (source population), or in related

⁴ Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378, 27.12.2006, p. 1.

⁵ OJ C 243, 24.9.2008, p. 1.

36 conditions or with related medicinal products, to make inferences for another
37 subgroup of the population (target population), or condition or product, thus reducing
38 the need to generate additional information (types of studies, design modifications,
39 number of patients required) to reach conclusions for the target population, condition
40 or medicinal product.

41 **2. FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT ON OR** 42 **MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND** 43 **REQUESTS FOR WAIVERS AND DEFERRALS**

44 **2.1. General principles and format**

45 The particulars and documents accompanying an application for agreement on or modification
46 of a paediatric investigation plan or a request for waiver or deferral should be presented in
47 accordance with this guideline. The application should consist of the following sections:

- 48 • Part A: Administrative and product information
- 49 • Part B: Overall development of the medicinal product, including information on the
50 conditions
- 51 • Part C: Application for a product-specific waiver
- 52 • Part D: Paediatric investigation plan
- 53 • Part E: Request for deferral
- 54 • Part F: Annexes.

55 The same application format should be used, whether requesting agreement on a paediatric
56 investigation plan, a waiver, a deferral, or a combination thereof. Sections and/or subsections
57 which are not relevant for the specific application can be left empty.

58 The application should be based on all available information relevant to the evaluation,
59 whether favourable or unfavourable to the product and its development. This includes details
60 of any incomplete or discontinued pharmaco-toxicological test or clinical study or trial
61 relating to the medicinal product, and/or completed trials concerning indications not covered
62 by the application.

63 It is acknowledged that the amount of available information relevant to applications will differ
64 substantially, depending on whether a medicinal product is in early clinical development or
65 already has a marketing authorisation and is being investigated for new or extended uses.

66 An application falling under the requirements of Article 7 or 8 of the Paediatric Regulation
67 should cover all subsets of the paediatric population with a condition unless there are grounds
68 for a waiver. The paediatric population is defined in Article 2 of the Paediatric Regulation as
69 ‘that part of the population aged between birth and 18 years’. This is understood to mean up
70 to but not including 18 years. The paediatric population encompasses several subsets, defined

71 for example in international guidelines⁶: the pre-term and term neonate from 0 to 27 days, the
72 infant or toddler from 1 month to 23 months, the child from 2 years to 11 years and the
73 adolescent from 12 up to 18 years. However, when it is considered more appropriate to use
74 different subsets (e.g. based on sex or pubertal development) this may be acceptable but the
75 choice of subsets should be explained and justified.

76 A paediatric investigation plan for a paediatric use marketing authorisation may be limited to
77 certain paediatric subsets.

78 All conditions that will be part of a single regulatory submission should be covered by the
79 application. Applications for products falling within the scope of Article 8 of the Paediatric
80 Regulation should cover both the existing and the new indications, pharmaceutical forms and
81 routes of administration. In this case one comprehensive paediatric investigation plan should
82 be included in the application.

83 The application may include a request for a product-specific waiver either in all subsets of the
84 given condition, or in some of them. Additionally, a paediatric investigation plan may include
85 a request for deferring some or all of the measures, in some or all subsets.

86 The European Medicines Agency (hereinafter ‘the Agency’) may publish templates or online
87 forms that follow the structure of this guideline. Procedural advice is available on the
88 Agency’s website (www.ema.europa.eu). Prospective applicants may also request
89 presubmission meetings, to facilitate successive validation and assessment of the application.

90 **2.2. Part A: Administrative and product information**

91 All sections of Part A should be completed; where information is not available, this should be
92 stated.

93 *2.2.1. Name or corporate name and address of the applicant and contact person*

94 The name and address of the applicant should be provided, together with the person
95 authorised to communicate with the Agency on behalf of the applicant.

96 In view of the fact that Agency decisions will be made public, the applicant is encouraged to
97 provide a contact point (telephone and email) for enquiries from interested parties that the
98 Agency will then make public with its decisions. Personal email addresses should be avoided.

99 Where the applicant qualifies as a micro, small or medium-sized enterprise within the
100 meaning of Commission Recommendation 2003/361/EC⁷ this should be stated.

101 *2.2.2. Name of the active substance*

102 The active substance should be stated by its recommended International Non-proprietary
103 Name (INN), accompanied by its salt or hydrate form if relevant. If no recommended INN
104 exists, the European Pharmacopoeia name should be provided or, if the substance is not in the
105 European Pharmacopoeia, the usual common name should be provided. In the absence of a
106 common name, the exact scientific designation should be given. Substances not having an

⁶ ICH Guideline E11 available at: www.ich.org.

⁷ OJ L 124, 20.5.2003, p. 36.

107 exact scientific designation should be described by a statement of how and from what they
108 were prepared, supplemented where appropriate by any relevant details.

109 In addition to the common name or scientific designation, the applicant may also submit the
110 company or laboratory code.

111 Considering the timing for submission of applications, only preliminary names of the active
112 substance might be provided.

113 The full scientific designation may be considered commercially confidential. In this case, the
114 applicant can propose an abridged name in the form of 'a derivative of parent compound [X]',
115 to be used in any published information or decision concerning the application.

116 2.2.3. *Type of product*

117 The type of product for which the application is made (e.g. a chemical entity, a biological
118 product, a vaccine, a gene therapy product, a somatic cell therapy medicinal product) should
119 be specified. In addition, where possible the pharmacological target and mechanism of action
120 should be specified. Where a pharmacotherapeutic group and Anatomical Therapeutic
121 Chemical (ATC) code have been assigned, these should be included. For products not yet
122 authorised in the European Union, or for authorised products where a new indication is
123 proposed for development, the condition, whether in adults or children, that the medicinal
124 product is intended to diagnose, prevent or treat, as envisaged at the time of submission,
125 should be named by the applicant, following an agreed classification system, such as
126 MedDRA.

127 2.2.4. *Details of the medicinal product*

128 Information on all different pharmaceutical forms and formulations under development,
129 irrespective of future use in the paediatric population, should be provided. For products being
130 developed for paediatric use marketing authorisations, information on the proposed strength,
131 pharmaceutical form and route of administration should be provided.

132 2.2.5. *Marketing authorisation status of the medicinal product*

133 Information on the marketing authorisation status of the medicinal product should be provided
134 in tabular format.

135 For medicinal products authorised in the EU the marketing authorisation status including
136 information on all authorised indications, strengths, pharmaceutical forms and routes of
137 administration should be provided and, regarding the authorisation status outside the EU, only
138 information on authorisations in children should be included.

139 For products being developed for paediatric use marketing authorisations, information should
140 be provided on authorised medicinal products in the EU containing the same active substance.

141 For medicinal products not yet authorised in the EU the marketing authorisation status outside
142 the EU should be provided.

143 Details of any regulatory action to restrict for safety reasons the use of the medicinal product
144 outside the EU should be provided. This will include any product withdrawal, restriction of
145 indication or new contraindication for the medicinal product.

146 2.2.6. *Advice from any regulatory authority relevant to the development in the paediatric*
147 *population*

148 The Agency should be provided with any decisions, opinions or advice (including scientific
149 advice) given by competent authorities, including those of non-EU countries, on the paediatric
150 development of the medicinal product. This should include any written request for paediatric
151 information issued by a regulatory body. A copy of any relevant documents should be
152 annexed to the application.

153 2.2.7. *Orphan medicine status in the EU*

154 For orphan designated products, the number in the European Union Register of Orphan
155 Medicinal Products should be provided. If orphan designation is being sought this should be
156 indicated, and for pending applications the EMA Orphan Designation Procedure Number
157 should be provided.

158 2.2.8. *Planned application for marketing authorisation/line extensions/variation*

159 The planned submission date for the marketing authorisation (or variation/extension
160 application, as appropriate) should be provided, together with an indication of whether the
161 application is planned to be submitted via the centralised procedure or the procedures
162 provided for by Directive 2001/83/EC⁸.

163 For medicinal products not yet authorised, which will fall under the requirements of Article 7
164 of the Paediatric Regulation, the date of completion of adult pharmacokinetic studies should
165 be provided. When an application is submitted later than upon completion of the human
166 pharmacokinetic studies in adults, a justification should be provided in this section.

167 2.2.9. *Application summary*

168 Applications for paediatric investigation plans or waivers should contain an application
169 summary, not longer than 750 words, written in accordance with a template made available by
170 the Agency.

171 2.2.10. *Table of translations of the Agency decision*

172 If the Agency decision is requested in an official EU language other than English then the
173 name of the active substance, the condition, the pharmaceutical form and route of
174 administration should be provided in that language.

175 **2.3. Part B: Overall development of the medicinal product, including information on**
176 **the conditions**

177 For medicinal products being developed for applications that will fall under the requirements
178 of Articles 7 and 8 of the Paediatric Regulation, Part B should list for each existing indication
179 and proposed condition/indication, and each subset of the paediatric population, how the
180 requirements of Articles 7 and 8 will be met.

181 Applicants should provide a general justification of the application submitted, including the
182 methodology chosen to identify potential conditions of paediatric need.

⁸ OJ L 311, 28.11.2001, p. 67.

183 This part should also include a description of the condition in the paediatric population,
184 including their similarity between adult and paediatric populations and within the different
185 paediatric subsets, prevalence, incidence, diagnosis and treatment methods, and alternative
186 treatments. For common, well-described paediatric conditions, reference can be made to
187 paediatrics textbooks without submitting detailed information. Furthermore, detailed
188 information on the condition in adults need not be provided.

189 Where the medicinal product is developed for use in children only, some of the information
190 requested in Part B may not be available and this should be clearly indicated.

191 *2.3.1. Discussion on similarities and differences in the condition between populations, and*
192 *pharmacological rationale*

193 Similarities and differences in the condition. The application should briefly discuss any
194 potential differences or similarities in the condition between the adult and the paediatric
195 populations and/or between the different paediatric subsets.

196 This should be discussed with a view to extrapolation of efficacy and/or pharmacokinetics,
197 between adults and children, and the various paediatric subsets. Differences in aetiology,
198 severity, symptoms, evolution, prognosis and response to therapy should be addressed where
199 applicable.

200 Pharmacological rationale and explanation. A sufficiently detailed description of the
201 pharmacological properties and of the known or suspected mechanism of action should be
202 provided. The potential paediatric use of the product, based on the characteristics of the
203 product, should be discussed by the applicant in the therapeutic area of the proposed
204 indication in adults, and particularly in the relevant conditions. In addition, data/assumptions
205 and a discussion of the impact of maturation aspects of pharmacokinetics should be provided
206 where applicable.

207 *2.3.2. Current methods of diagnosis, prevention or treatment in paediatric populations*

208 For each condition covered by the application, the diagnosis, prevention and treatment
209 interventions that are available in the EU should be identified, making reference to scientific
210 literature or other relevant information. This should include unauthorised treatment methods,
211 if they represent the standard of care, for example if they are mentioned in internationally
212 recognised treatment guidelines. This should be presented in tabular format for ease of
213 reference.

214 Of the available treatments identified, in the case of authorised medicinal products, the list
215 should include those authorised by the national authorities and those authorised under the
216 centralised procedure. This can be presented as an overview table. Information on generic
217 medicinal products need not be provided.

218 For medical devices, the invented name and the approved use should be provided if placed on
219 the market in the EU.

220 If methods for diagnosis, prevention or treatment of the condition in question have been
221 included in the inventory of therapeutic needs established pursuant to Article 43 of the
222 Paediatric Regulation then this information should be highlighted.

223 2.3.3. *Significant therapeutic benefit and/or fulfilment of therapeutic need*

224 The Paediatric Committee will assess whether the specific medicinal product is expected to be
225 of significant therapeutic benefit to children and/or to fulfil a therapeutic need in children. The
226 application should include a comparison of the medicinal product which is the subject of the
227 application with the current methods of diagnosis, prevention or treatment of the conditions
228 that are the subject of the intended indications in children.

229 When considering significant therapeutic benefit the Paediatric Committee will take into
230 account the nature and the seriousness of the condition to be treated (or diagnosed or
231 prevented) and the available data on the medicinal product concerned. Significant therapeutic
232 benefit could be based on one or more of the following:

- 233 (a) reasonable expectation of safety and efficacy for a marketed or new medication to
234 treat a paediatric condition, where no authorised paediatric medicinal product is on
235 the market;
- 236 (b) expected improved efficacy in a paediatric population, compared to the current
237 standard of care for the treatment, diagnosis or prevention of the condition
238 concerned;
- 239 (c) expected improvement in safety, in relation to either adverse reactions or potential
240 medication errors in a paediatric population compared to the current standard of care;
- 241 (d) improved dosing scheme or method of administration (e.g. number of doses per day,
242 oral compared to intravenous administration, reduced treatment duration) leading to
243 improved safety, efficacy or compliance;
- 244 (e) availability of a new clinically relevant age-appropriate formulation or
245 pharmaceutical form;
- 246 (f) availability of clinically relevant and new therapeutic knowledge for the use of the
247 medicinal product in the paediatric population leading to improved efficacy or safety
248 of the medicinal product in the paediatric population;
- 249 (g) different mechanism of action with potential advantage for the paediatric population
250 in terms of improved efficacy or safety;
- 251 (h) unsatisfactory nature of existing treatments and need for alternative methods with an
252 improved expected benefit-risk balance;
- 253 (i) expected improvement in the quality of life of the child.

254 As experience with the use of the medicinal product in the paediatric population might not be
255 available or might be very limited at the time of submission of the application, significant
256 therapeutic benefit might also be based on well-justified and plausible assumptions. The
257 application should explore these assumptions based on reasoned arguments and relevant
258 literature.

259 If the therapeutic need is included in the inventory of therapeutic needs pursuant to Article 43
260 of the Paediatric Regulation, the application should refer to the inventory.

261 **2.4. Part C: Applications for product-specific waivers**

262 2.4.1. *Overview of the waiver request*

263 A waiver may be issued with reference either to one or more specified subsets of the
264 paediatric population, or to one or more specified conditions, or to a combination of both.
265 Requests for product-specific waivers should clearly define their scope in terms of paediatric
266 subset and indication.

267 A product-specific waiver may not be required if the proposed indication falls within a
268 condition (and subset of the paediatric population) already covered by a class waiver. Where
269 the submission is only partially covered by class waiver, but a product-specific waiver is
270 necessary to satisfy the requirements, the class waivers should be referred to when specifying
271 the scope of the product-specific waiver.

272 Companies may request the Agency to give advance confirmation of the applicability of a
273 class waiver to a proposed development of a medicinal product in one or more adult
274 conditions.

275 2.4.2. *Justification for a product-specific waiver*

276 2.4.2.1. Applications based on a likely lack of safety or efficacy in part or all of the paediatric
277 population

278 In accordance with Article 11(1)(a) of the Paediatric Regulation a waiver may be granted if
279 ‘the specific medicinal product or class of medicinal products is likely to be ineffective or
280 unsafe in part or all of the paediatric population’. On this basis, a request for a waiver may be
281 based on a pharmaceutical rationale or (preliminary) data suggesting lack of efficacy or safety
282 in the paediatric population. The application should take account, for the different paediatric
283 subsets, of the seriousness of the condition and the availability of other methods as stated in
284 Part B. All available evidence should be submitted describing the lack of efficacy in the
285 paediatric population as a whole or in subsets, as applicable. The justification should be based
286 on effects observed in non-clinical models, studies and trials, when available.

287 The justification for a waiver based on evidence that the product is unsafe may differ
288 depending on the existing experience with the product. Justification for a waiver on these
289 grounds may include the pharmacological properties of the product or class of product, results
290 of non-clinical studies, clinical trials or post-marketing data. The applicant should specify
291 whether a specific safety issue is known or suspected.

292 At an early stage of development, the absence of any available data on the safety or efficacy
293 in the paediatric population will not be accepted as the sole justification for a waiver.

294 2.4.2.2. Applications based on the disease or condition not occurring in the specified
295 paediatric subset

296 In accordance with Article 11(1)(b) of the Paediatric Regulation a waiver may be granted if
297 ‘the disease or condition for which the specific medicinal product or class is intended occurs
298 only in adult populations’. On this basis, a justification for a waiver may be based on a
299 detailed description of the incidence or prevalence of the condition in different populations.
300 For waivers covering the totality of the paediatric population, the justification should
301 particularly focus on the earliest age of onset of the condition. For waivers for specific subsets

302 of the paediatric population, the justification should focus on the incidence or prevalence in
303 the different paediatric subsets delineated in Part B.

304 2.4.2.3. Applications based on lack of significant therapeutic benefit

305 In accordance with Article 11(1)(c) of the Paediatric Regulation a waiver may be granted if
306 'the specific medicinal product does not represent a significant therapeutic benefit over
307 existing treatments for paediatric patients'. On this basis, the justification for a waiver may be
308 based on a lack of significant therapeutic benefit.

309 Where a waiver based on a lack of significant therapeutic benefit is requested, justification for
310 such a waiver should be based on a detailed discussion of the existing treatment methods.
311 Reference can be made to the discussion under point 2.3.3.

312 In particular, when existing medicinal products are authorised for use in children, applicants
313 intending to request a waiver on this ground should justify in detail why the new product
314 would be devoid of significant benefit over the existing treatments.

315 If applicants intend to claim a lack of significant benefit due to non-feasibility of measures,
316 appropriate and detailed justification should be provided to support the claim.

317 **2.5. Part D: Paediatric investigation plan**

318 Part D should focus specifically on the development of the medicinal product for the
319 paediatric population. While applicants can discuss possible choices, there is no need to
320 propose separate alternative developments in the application.

321 *2.5.1. Existing data and overall strategy proposed for the paediatric development*

322 2.5.1.1. Paediatric investigation plan indication

323 The proposed indication should be established for the paediatric subsets included in the
324 paediatric investigation plan. This part should specify whether the medicinal product is
325 intended for the diagnosis, prevention or treatment of the conditions in question.

326 2.5.1.2. Selected paediatric subsets

327 The age ranges to be studied should be justified, and may vary depending on the
328 pharmacology of the product, the manifestation of the condition in various age groups and
329 other factors. In addition to age, the classification of the paediatric population may be based
330 on other variables, such as gestational age, pubertal stages, gender and renal function.

331 2.5.1.3. Information on the quality, non-clinical and clinical data

332 The application should outline the development of the medicinal product, including the
333 pharmaceutical development which is relevant for paediatric development, completed clinical
334 studies in adults and the results when available. A brief outline of the planned studies in adults
335 should also be provided. This information may be provided in tabular format.

336 The full study reports of completed non-clinical and clinical studies do not need to be
337 provided; a summary of the results and a discussion of the implications for paediatric
338 development should be sufficient. Full reports should be made available upon request. The

339 application should take into account any existing scientific guidance/advice and standard
340 paediatric investigation plans published by the Agency and justify any deviation for the
341 paediatric development.

342 In addition, the application should include a review of any information on the product in the
343 paediatric population, making reference to scientific and medical literature or other relevant
344 information, such as reports on use outside the terms of a marketing authorisation, medication
345 errors, accidental exposures, or known class effects.

346 2.5.2. *Paediatric formulation development*

347 2.5.2.1. General strategy

348 This section should address selected aspects related to the administration of the product to the
349 relevant paediatric subsets.

350 The addition of a paediatric indication may result in the need for a new pharmaceutical form,
351 for example a dispersible form rather than a large tablet, or a microtablet of a new strength,
352 because the existing pharmaceutical form, excipients, or strength may be unsuitable for use in
353 all or part of the relevant paediatric populations. This means that the suitability of the existing
354 formulation and pharmaceutical forms should always be discussed in the paediatric
355 investigation plan. Consideration should be given to any ethnic or cultural difference in
356 palatability, route of administration, acceptable dosage forms and excipients.

357 The discussion will take into account the existing or proposed pharmaceutical development of
358 the product and should address critical issues, such as:

- 359 • the need for specific formulations or pharmaceutical forms in relation to the chosen
360 paediatric subsets/age groups, and discussion of the benefit of the chosen formulation
361 or form;
- 362 • potential issues in relation to excipients to be used in the paediatric population;
- 363 • administration of the medicine to paediatric subsets (e.g. palatability, use of specific
364 administration devices, ability to mix with food);
- 365 • precision of dose delivery in the case of solid dosage forms, when breakable tablets
366 are proposed for paediatric use;
- 367 • timeframe for the development of an age-appropriate formulation/pharmaceutical
368 form, where required.

369 If it is not possible, based on scientific justifications, to develop a formulation/pharmaceutical
370 form which is relevant and acceptable for paediatric use on an industrial scale, the applicant
371 should state how it intends to facilitate the industry-verified or extemporaneous preparation of
372 an individual ready-for-use paediatric formulation.

373 2.5.2.2. Outline of each of the planned and/or ongoing studies and steps in the
374 pharmaceutical development

375 The application should contain in tabular format a list of planned and/or ongoing measures
376 intended to address the issues discussed under point 2.5.2.1. This list should consist of the
377 proposed key elements in accordance with the annex to this guideline.

378 If the strategy is to create a new pharmaceutical form (e.g. new dosage form, or new route of
379 administration) then the necessary pharmaceutical development studies may need to be more
380 extensive. Agency guidelines in this area should be consulted to decide which measures could
381 be relevant within the strategy proposed.

382 Proposed measures of particular relevance to the development of paediatric products include:

- 383 • compatibility with paediatric administration systems, e.g. medical devices;
- 384 • taste-masking and palatability.

385 2.5.3. *Non-clinical studies*

386 2.5.3.1. General strategy

387 This section should discuss the strategy for the non-clinical development which is needed to
388 support paediatric use in addition to classical non-clinical development or to already existing
389 data. If human safety data and previous animal studies are considered insufficient for
390 reassurance on the likely safety profile in the intended paediatric age group, juvenile animal
391 studies should be considered on an individual basis.

392 The standard non-clinical development should not be submitted or discussed unless it brings
393 relevant information to the paediatric development and is not covered elsewhere in the
394 application package (i.e. the investigator brochure).

395 The following aspects should be discussed, taking into consideration existing scientific
396 guidance:

397 (a) pharmacology:

- 398 • the need for proof of concept for the use in paediatric populations, for example using
399 non-clinical *in vitro* and/or *in vivo* models;
- 400 • the need for pharmacodynamic studies in children (e.g. to establish a dose
401 relationship for a pharmacodynamic endpoint, if there is a reliable animal model to
402 justify the choice of the most relevant species for potential juvenile animal studies);
- 403 • the need for paediatric safety pharmacology (studies using non-clinical *in vitro*
404 and/or *in vivo* models to investigate specific functions of the physiological system);

405 (b) toxicology:

- 406 • the need for toxicity studies to address specific endpoints, e.g. neurotoxicity,
407 immunotoxicity or nephrotoxicity at a particular developmental phase.

408 2.5.3.2. Summary of each of the planned and/or ongoing non-clinical studies

409 A tabular list should be provided, with the proposed non-clinical measures. This list should
410 consist of the proposed key elements for the non-clinical measures in accordance with the
411 annex to this guideline.

412 2.5.4. *Paediatric clinical studies*

413 2.5.4.1. General aspects

414 This section should discuss and justify the strategy for the clinical paediatric development, in
415 relation to the development in adults where applicable and in relation to existing data and the
416 potential to extrapolate. This should include critical aspects of study design and should
417 present the strengths, advantages and disadvantages of the proposed clinical development.

418 In this section, the application should also discuss possible complete or partial extrapolation
419 from adult data to paediatric patients and between paediatric subsets. The interrelation in
420 terms of common studies, data and timelines between development in adults and paediatric
421 populations should be explained. If extrapolation is a substantial component of the proposed
422 development, a specific extrapolation protocol should be described in the list of measures.
423 Trials should be performed in the least vulnerable groups whenever possible (i.e. in adults
424 rather than in children, in older children rather than younger ones). If results cannot be
425 extrapolated to younger groups, this should be justified.

426 A discussion on how dosing in very young and young children is determined and verified
427 should be included where necessary.

428 2.5.4.2. Paediatric pharmacokinetic/pharmacodynamics studies

429 The following aspects should be considered, where relevant:

430 (a) pharmacodynamic studies:

- 431 • pharmacodynamic differences between adult and paediatric populations (e.g.
432 influence of maturation of receptors and/or systems);
- 433 • use of pharmacodynamic modelling;
- 434 • discussion of any biomarkers for pharmacokinetics/pharmacodynamics;
- 435 • use of the pharmacodynamic approach, particularly when pharmacokinetics cannot
436 be measured;

437 (b) pharmacokinetic studies:

- 438 • possibility to use sparse pharmacokinetic sampling;
- 439 • use of population pharmacokinetics;
- 440 • discussion of age groups where more extensive studies are needed, e.g. due to
441 expected high kinetic variability;

442 • pharmacogenetics.

443 2.5.4.3. Clinical efficacy and safety studies

444 The following aspects should be considered, where relevant:

445 • discussion of the need for specific dose-finding studies;

446 • discussion of the selected efficacy and/or safety endpoints (primary or secondary), in
447 each of the relevant paediatric subsets;

448 • discussion of issues of relevance across the proposed studies, such as use of placebo
449 or active control, age appropriateness of endpoints, use of surrogate markers, use of
450 alternative study design and analysis, potential need for short-term and long-term
451 safety studies and differential risks by age group.

452 Any potential concern for the long-term safety or efficacy in the paediatric population should
453 always be discussed in the paediatric investigation plan application. If such studies are
454 considered necessary, the details should be provided in the risk management plan, but would
455 not normally form part of the agreed paediatric investigation plan.

456 Finally, specific measures proposed to protect the paediatric population involved in
457 development, for example the use of less invasive methods, should be discussed where
458 relevant.

459 Issues related to the feasibility of the proposed studies (e.g. recruitment capacity) should be
460 presented and discussed.

461 2.5.4.4. Summary table of all planned and/or ongoing clinical studies in the paediatric 462 population

463 A tabular list should be provided, with the proposed clinical measures. This list should consist
464 of the proposed key elements for clinical studies in accordance with the annex to this
465 guideline.

466 The table should propose timelines for initiation and completion of each measure, including
467 specific dates (month and year) or ranges of up to six months, and should specify whether a
468 deferral is being requested for the initiation and/or completion of each measure. Timelines for
469 initiation may also be linked to the completion of a study in adults ('x months after completion
470 of study y') or a measure in the paediatric investigation plan.

471 As completion of a measure (trial) is understood as the date of the last visit of the last subject
472 included, the timelines should include a reasonable amount of time to complete, analyse and
473 report the studies to be included in the marketing authorisation application, since the final
474 (complete) study report is necessary for the operation of the compliance check.

475 2.5.4.5. Details of the planned and/or ongoing clinical studies

476 In order to help the Paediatric Committee to understand the proposed measures, the applicant
477 may in addition provide more detailed information, such as a full study protocol.

478 Additional information, as appropriate to the stage of product development and in addition to
479 the proposed key elements, may be provided:

- 480 • justification of type of study, study design and methodology;
- 481 • main objective of the study;
- 482 • justification of the dose of the proposed product and its regimen, and of the type of
483 control (e.g. placebo or active control, with dose to be used);
- 484 • information on the location of the study (where scientifically justified);
- 485 • description of the sample size/power calculation (as appropriate; with expected effect
486 size in children) used to determine the proposed number of subjects (M/F). This
487 discussion should include, whenever possible, a sensitivity analysis (a tabulation
488 with varying assumptions and statistical parameters, and the resulting sample sizes);
- 489 • justification of the relevant age groups or subsets included in the study (and of
490 staggered inclusion where applicable);
- 491 • justification of the proposed duration of treatment (and duration of post-treatment
492 observation if included in the study);
- 493 • proposed main inclusion/exclusion criteria;
- 494 • justification of the choice of outcome parameters/endpoints (primary, secondary);
- 495 • justification and, if needed, a more detailed description of statistical methods than the
496 one contained in the key elements;
- 497 • discussion of options in the event of recruitment issues.

498 **2.6. Part E: Request for deferral**

499 With reference to the timelines stated in Part D, any request for deferral of the start or the
500 completion of measures should make clear the indication, route of administration and
501 pharmaceutical form to which the deferred timeline relates. When requesting a deferral, the
502 application should also specify the age group to which it applies. For timelines, specific
503 months and years should be given, and timelines may also be expressed in relation to the
504 development in adults.

505 Requests for deferrals should be justified on scientific and technical grounds or on grounds
506 related to public health. The Paediatric Regulation requires that a deferral be granted when:

- 507 • it is appropriate to conduct studies in adults prior to initiating studies in the paediatric
508 population;
- 509 • studies in the paediatric population will take longer to conduct than studies in adults.

510 Particular emphasis should be placed on the timing of the measures compared to the
511 development for adults, as expressed for example in the ICH guideline (E11).

512 **2.7. Part F: Annexes**

513 The annexes to the application should include the following documents, if available:

- 514 • references (i.e. published literature);
- 515 • the investigator brochure (latest version), or full protocols of the proposed studies;
- 516 • the latest approved summary of product characteristics and risk management plan for
517 a product already authorised;
- 518 • a letter of authorisation for the person authorised to communicate on behalf of the
519 applicant;
- 520 • a copy of any scientific advice given by the EMA Committee on Human Medicinal
521 Products;
- 522 • a copy of any scientific advice given by any EU national competent authority;
- 523 • a copy of any written request by the United States Food and Drug Administration
524 and/or of any advice/opinion/decision relating to paediatric information given by a
525 regulatory agency outside the EU;
- 526 • a copy of any Commission decision on orphan designation;
- 527 • the reference number or a copy of any previous EMA decision on paediatric
528 investigation plans or a negative opinion of the Paediatric Committee on such plans.

529 **2.8. Modification of an agreed paediatric investigation plan**

530 As the development of medicinal products is a dynamic process dependent on the result of
531 ongoing studies, provision is made in Article 22 of the Paediatric Regulation for modifying an
532 agreed plan where necessary. Those modifications are required where key elements of the
533 paediatric investigation plan are unworkable or no longer appropriate.

534 Submission of an application to modify the paediatric investigation plan, or a request for
535 deferral or a waiver will be particularly important if the new information may have an impact
536 on the nature or timing for completion of one of the key elements in the Agency decision on
537 the paediatric investigation plan.

538 In the case of an application for modification of a paediatric investigation plan, the content of
539 the application should follow the same structure as for an initial paediatric investigation plan,
540 but only relevant sections supporting the change should be completed. The application should
541 provide the reference of the previous paediatric investigation plan decision.

542 **Consultation item No 1: Do you have any comments on the format and content of**
543 **applications for agreement on or modification of a paediatric investigation plan and**
544 **requests for waivers or deferrals?**

545 **3. OPERATION OF THE COMPLIANCE CHECK**

546 Compliance with the requirements of Articles 7 and 8 of the Paediatric Regulation and the
547 compliance of applications for paediatric use marketing authorisations are checked by the
548 competent authorities. These compliance checks are described in Articles 23 and 24 of the
549 Paediatric Regulation. Article 23 specifies the timing of the compliance check, provides for
550 the possibility of an opinion of the Paediatric Committee on compliance and clarifies when
551 and by whom this opinion can be requested. Pursuant to Article 23(3), second subparagraph,
552 Member States must take account of the opinion of the Paediatric Committee.

553 Compliance is checked by the competent authorities as follows:

- 554 • pursuant to Article 23 of the Paediatric Regulation, compliance is checked at
555 validation for applications for marketing authorisation or variation. Non-compliance
556 of these applications will lead to non-validation of the application;
- 557 • pursuant to Article 24 of the Paediatric Regulation, detection of non-compliance
558 during the scientific assessment of a valid application will result in non-inclusion in
559 the marketing authorisation of the compliance statement referred to in Article 28(3);
560 the medicinal product will not be eligible for the rewards and incentives provided for
561 in Articles 36, 37 and 38 of the Paediatric Regulation.

562 The determination of compliance described above will include:

- 563 • whether or not the documents submitted pursuant to Article 7(1) of the Paediatric
564 Regulation cover all subsets of the paediatric population;
- 565 • for applications falling within the scope of Article 8 of the Paediatric Regulation,
566 whether the documents submitted pursuant to Article 7(1) cover the existing and the
567 new indications, pharmaceutical forms and routes of administration; and
- 568 • whether all of the measures in an agreed paediatric investigation plan have been
569 carried out in accordance with the key elements specified in the decision approving
570 the paediatric investigation plan. The measures checked for compliance are those that
571 are part of the condition covering an indication for which an application for
572 marketing authorisation is made and that are not deferred.

573 Any necessary modification of the paediatric investigation plan should take place before the
574 submission of the application for marketing authorisation or variation.

575 Compliance can be judged only if final study reports are provided. To facilitate the work of
576 the competent authorities and, when appropriate, the Paediatric Committee in reaching an
577 opinion on compliance, presentation of a compliance report at the time of the submission of
578 the application is encouraged.

579 For medicinal products that fall under the scope of Articles 7 or 8, the compliance report
580 should indicate in the form of a table how each subset of the paediatric population and, for
581 applications falling under Article 8 of the Paediatric Regulation, how each of the existing and
582 new indications, pharmaceutical forms and routes of administration have been covered by the
583 documents referred to in Article 7(1) of the Paediatric Regulation. A separate table should be
584 included covering the applicant's position on compliance with the key elements and, when
585 submitted with the marketing authorisation application, a cross-reference for each key

586 element of the paediatric investigation plan to the location within the relevant module in that
587 marketing authorisation application. If a paediatric investigation plan has been modified, the
588 table should be based on the latest decision of the Agency.

589 It should be noted that:

590 • the relevant competent authority or the Agency will perform a detailed check on each
591 key element of the Agency decision on the paediatric investigation plan against what
592 has actually been submitted;

593 • because the decision on the paediatric investigation plan will include the key
594 elements for each of the measures, the applicant for marketing authorisation or
595 variation will need to comply with each item;

596 • when conditional language such as ‘could’, or ‘such as’ is used in the opinion, then
597 compliance may be confirmed even if these measures were not followed as
598 suggested.

599 When only some measures referred to in the Agency decision had to be completed, the
600 Paediatric Committee will adopt a letter confirming or denying (interim) compliance with
601 those measures. In all cases, the grounds for accepting or denying compliance will be detailed
602 in a report adopted by the Committee.

603 Where the measures in a paediatric investigation plan contain no study completed before the
604 entry into force of Regulation (EC) No 1901/2006 (26 January 2007), the statement of
605 compliance referred to in Article 28(3) of the Paediatric Regulation will be the following:

606 ‘The development of this product has complied with all measures in the agreed
607 paediatric investigation plan [reference number]. All studies were completed after the
608 entry into force of Regulation (EC) No 1901/2006’.

609 Where the measures in a paediatric investigation plan contain some studies completed before
610 the entry into force of Regulation (EC) No 1901/2006, the statement of compliance referred to
611 in Article 28(3) of the Paediatric Regulation will be the following:

612 ‘The development of this product has complied with all measures in the agreed
613 paediatric investigation plan [reference number]. For the purpose of the application
614 of Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed
615 paediatric investigation plan were completed after the entry into force of that
616 Regulation’.

617 The statement of compliance must be included in the marketing authorisation together with
618 other technical information that forms part of the marketing authorisation (‘technical
619 dossier’). For reasons of legal certainty, the competent authorities in the Member States or, in
620 the case of centralised marketing authorisations, the Agency must provide the marketing
621 authorisation holder with confirmation that the compliance statement is included in the
622 technical dossier of the marketing authorisation.

623 **Consultation item No 2: Do you have any comments on the operation of the compliance**
624 **check and/or the compliance statement?**

625 **4. CRITERIA FOR ASSESSING THE SIGNIFICANCE OF STUDIES STARTED**
626 **BEFORE AND COMPLETED AFTER THE ENTRY INTO FORCE OF THE**
627 **PAEDIATRIC REGULATION**

628 **4.1. Background**

629 For studies started before the entry into force of the Paediatric Regulation to qualify for the
630 rewards and incentives provided for in Articles 36, 37 and 38 of the Regulation, they need to
631 be completed after the entry into force of the Regulation and to be judged significant
632 (Article 45(3) of the Paediatric Regulation). The statement of compliance referred to in
633 Article 28(3) of the Paediatric Regulation will indicate whether those studies are considered
634 significant within the meaning of Article 45(3) of the Regulation.

635 **4.2. Assessment criteria**

636 In general, the significance of studies is determined by the clinical relevance of data generated
637 for the paediatric population rather than by the number of studies. In exceptional cases, a set
638 of non-significant studies might be considered as significant if the results taken together are
639 expected to provide important and clinically relevant information.

640 A study will be considered as completed after the entry into force of the Paediatric Regulation
641 when the last visit of the last patient has occurred, as planned in the latest version of the
642 protocol (as submitted to the competent authorities), and falls after the date of entry into force
643 of the Paediatric Regulation. Open extensions of studies consisting of treatment maintenance
644 for patients included will not be considered as continuing after the entry into force, if this was
645 not part of the protocol submitted to the relevant competent authorities.

646 The Agency or the competent authorities will assess the significance of each study proposed
647 in a paediatric investigation plan on a case-by-case basis. However, the examples below are
648 provided as a guide to the assessment of the significance of studies.

649 The following study types will generally be considered as significant:

- 650 (1) comparative efficacy studies (randomised/active control or placebo);
- 651 (2) dose-finding studies;
- 652 (3) prospective clinical safety studies, if the results are expected to make a major
653 contribution to the safe use of the medicinal product in the paediatric population (this
654 includes studies on growth and development);
- 655 (4) studies to obtain a new age-appropriate formulation, if the formulation is expected to
656 be of clinical relevance for the safe and effective use of the medicinal product in the
657 paediatric population;
- 658 (5) PK/PD studies: pharmacokinetic/pharmacodynamic clinical studies if they are likely
659 to provide meaningful data that would avoid the need for a clinical efficacy study
660 and therefore spare the numbers of children who may need to be enrolled in a larger
661 trial.

662 In order to be considered as significant, the studies should normally cover several paediatric
663 subsets affected by the condition where sufficient data are not available, unless a waiver has

664 been granted. However, on a case-by-case basis, studies conducted in a single subset of the
665 paediatric population could be considered as significant if sufficiently extensive or if they
666 make an important contribution to treatment of children or if they are carried out in a subset
667 considered particularly difficult to study, for example neonates. Where sufficient data for one
668 or more of the paediatric subsets are already available, duplication of studies should be
669 avoided and therefore unnecessary studies will not be considered as significant.

670 **Consultation item No 3: Do you have any comments on the assessment criteria for**
671 **significant studies?**

672

ANNEX

673

Key elements

674

1. Paediatric formulation development

675

(a) Pharmaceutical form proposed for development for paediatric use

676

(b) Objectives for pharmaceutical development

677

(c) Timelines for completion

678

2. Non-clinical studies

679

(a) Type of study

680

(b) Objectives

681

(c) Test system/species

682

(d) Route of administration and doses

683

(e) Duration of dosing

684

(f) Timelines for completion

685

3. Paediatric clinical studies:

686

3.1 Paediatric pharmacokinetic/pharmacodynamic studies

687

(a) Type of study

688

(b) Objectives of study

689

(c) Study design

690

(d) Age group and population in which the study will be conducted

691

(e) Paediatric formulation(s) used in the study

692

(f) Dose ranges to be used in the PK studies

693

(g) Endpoints

694

(h) Modelling/simulation

695

(i) Sample size

696

(j) Timelines for completion

697

3.2 Efficacy and safety studies

698

(a) Type of study

- 699 (b) Objectives of the study
- 700 (c) Study design
- 701 (d) Age group and population in which the study will be conducted (including
702 minimum number of paediatric participants)
- 703 (e) Inclusion and exclusion criteria
- 704 (f) Endpoints (primary and main secondary)
- 705 (g) Timing of endpoint assessment
- 706 (h) Safety assessments (including timing)
- 707 (i) Statistical approach
- 708 (j) Timelines for completion

709 For deferred studies, time-limits for initiation are also part of the key elements.

710 **Consultation item No 4: Do you have any comments on the key elements of a paediatric**
711 **investigation plan? Is it appropriate to list key elements in this guideline or should key**
712 **elements only be specified in the individual decision of the Agency agreeing a specific**
713 **paediatric investigation plan?**

714 * * *

715 **Consultation item No 5: Please feel free to raise any other issues or make any comments**
716 **which have not been addressed in the consultation items above.**