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3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on similar biological medicinal products**  
5 **containing biotechnology-derived proteins as active**  
6 **substance: non-clinical and clinical issues**  
7 **Draft**

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10 This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-  
11 derived proteins as active substance: Non-clinical and clinical issues'  
12 (EMEA/CHMP/BMWP/42832/2005).

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<b>Keywords</b>	<b><i>similar biological medicinal product, recombinant proteins, non clinical studies, clinical studies, safety, pharmacovigilance, immunogenicity</i></b>
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## 41 **Executive summary**

42 The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as*  
43 *active substance: non-clinical and clinical issues* (EMA/CHMP/BMWP/42832/05 Rev.1) lays down the  
44 non-clinical and clinical requirements for a biological medicinal product claiming to be similar to  
45 another one already marketed ("biosimilar").

46 The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section  
47 addresses the requirements for pharmacokinetic, pharmacodynamic, and efficacy studies. The section  
48 on clinical safety and pharmacovigilance addresses clinical safety studies as well as the risk  
49 management plan with special emphasis on studying the immunogenicity of the biosimilar.

50 The current revision covers the following topics: a risk-based approach for the design of non-clinical  
51 studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population  
52 and choice of surrogate endpoints in efficacy trials; design of immunogenicity studies; and  
53 extrapolation of indication.

## 54 **1. Introduction**

55 A biosimilar is a biological medicinal product that contains a version of the active substance of an  
56 already authorised original biological medicinal product (reference medicinal product). A biosimilar  
57 demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological  
58 activity, safety and efficacy) based on a comprehensive comparability exercise.

59 The Marketing Authorisation (MA) application dossier of a biological medicinal product claimed to be  
60 similar to a reference medicinal product already authorised shall provide a full quality dossier together  
61 with the demonstration of comparability with the reference medicinal product by using appropriate  
62 physico-chemical and *in vitro* biological tests, non-clinical and clinical studies.

63 The quality issues relevant for demonstration of comparability for biosimilars containing recombinant  
64 DNA-derived proteins are addressed in the *Guideline on similar biological medicinal products containing*  
65 *biotechnology-derived proteins as active substances: quality issues* (EMA/CHMP/BWP/247713/2012).

66 The principles for the non-clinical and clinical parts of the comparability exercise are laid down in this  
67 guideline. Product-class-specific guidelines will supplement this guideline where a need is identified.

68 The nature and complexity of the reference product has an impact on the extent of the (non-)clinical  
69 studies to confirm biosimilarity. The differences observed in the physico-chemical and biological  
70 analyses will guide the planning of the (non-)clinical studies. Other factors that need to be taken into  
71 consideration are the mode of action of the active substance (e.g. receptor(s) involved) in all the  
72 licensed indications of the reference product and pathogenetic mechanisms involved in the disorders  
73 included in the therapeutic indications (e.g. mechanisms shared by various therapeutic indications).

74 The applicants should review data from the reference product on the predictive value of *in vitro*  
75 assays/animal models as well as correlations between dose/exposure and pharmacodynamics, on one  
76 hand, and pharmacodynamics and clinical response, on the other hand. The availability of suitable  
77 biomarkers may abbreviate the (non-)clinical development. The safety profile of the reference product  
78 will determine the focus of the safety studies both pre- and post-marketing.

79 CHMP has issued product-class-specific guidelines to facilitate the (non-)clinical development of  
80 biosimilar medicinal products in certain areas. However, the applicants have to fine tune their (non-)  
81 clinical studies according to the results of preceding physico-chemical and *in vitro* biological analyses of  
82 the biosimilar and the reference product.

## 83 2. Scope

84 This guideline addresses the general principles for the non-clinical and clinical development and  
85 assessment of the marketing authorisation applications of biosimilars containing recombinant proteins  
86 as active substance(s). This guideline does not address the comparability exercise for changes  
87 introduced in the manufacturing process of a given product (i.e. changes during development and  
88 post-authorisation).

## 89 3. Legal basis and relevant guidelines

90 Directive 2001/83/EC, as amended in particular in Directive 2001/83/EC Art 10(4) and Part II of the  
91 Annex I of Directive 2001/83/EC, as amended.

92 Directive 2010/63/EU on the protection of animals used for scientific purposes.

93 In addition, in particular, the following guidelines should be read in conjunction:

- 94 • Guideline on similar biological products (CHMP/437/04), the so-called 'overarching guideline'
- 95 • Guideline on similar biological medicinal products containing biotechnology-derived proteins as  
96 active substance – quality issues (EMA/CHMP/BWP/247713/2012)
- 97 • ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals  
98 (EMA/CHMP/ICH/731268/1998)
- 99 • ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for  
100 clinical trials (CPMP/ICH/363/96)
- 101 • ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- 102 • Guidelines on Good Pharmacovigilance Practices (GVP)
- 103 • ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting  
104 (CPMP/ICH/377/95)
- 105 • ICH E2E Note for guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)
- 106 • Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins  
107 (EMA/CHMP/BMWP/14327/2006)
- 108 • Guideline on Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use  
109 (EMA/CHMP/BMWP/86289/2010)
- 110 • Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins  
111 (CHMP/EWP/89249/2004)
- 112 • Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)
- 113 • Guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009)
- 114 • Product-class-specific guidelines on various biosimilar products

## 115 4. Non-clinical studies

116 Non-clinical studies should be performed before initiating clinical trials. A step-wise approach should be  
117 applied to evaluate the similarity of biosimilar and reference product. *In vitro* studies should be  
118 conducted first and a decision then made as to the extent of what, if any, *in vivo* work will be required.

119 It is important to note that design of an appropriate non-clinical study program requires a clear  
120 understanding of the reference product characteristics. Results from the physico-chemical and  
121 biological characterisation studies (i.e. comparability of the biosimilar to the reference product) should  
122 be reviewed from the point-of-view of potential impact on efficacy and safety.

123 The following approach may be considered and should be tailored to the product concerned on a case-  
124 by-case basis. The approach taken will need to be fully justified in the non-clinical overview.

#### 125 **4.1. Step 1: In vitro studies**

126 In order to assess any difference in biological activity between the biosimilar and the reference  
127 medicinal product, data from a number of comparative *in vitro* studies, some of which may already be  
128 available from quality-related assays, should normally be provided.

129 These studies could include relevant assays on:

130 - *Binding* to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-  
131 toxicological effects of the reference product.

132 - *Signal transduction and functional activity/viability* of cells known to be of relevance for the  
133 pharmaco-toxicological effects of the reference product.

134 The studies should be comparative in nature and should not just assess the response per se. The  
135 studies should evaluate parameters sensitive enough to detect differences. The studies should assess  
136 the concentration–activity/binding relationship between the biosimilar and the reference medicinal  
137 product covering a concentration range where differences are most sensitively detected. They should  
138 be performed with an appropriate number of batches of product representative of that intended for  
139 clinical use.

140 Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects  
141 known to be of relevance for the reference product and for the product class. Since *in vitro* assays  
142 may often be more specific and sensitive to detect differences between the biosimilar and the  
143 reference product than studies in animals, these assays can be considered as paramount for the non-  
144 clinical comparability exercise.

145 The applicant should justify that the *in vitro* assays used are predictive for the *in vivo* situation.

146 If the biosimilar comparability exercise indicates early on that there are significant differences between  
147 the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will  
148 eventually be established, a stand-alone development, should be considered instead.

#### 149 **4.2. Step 2: Determination of the need for in vivo studies**

150 It is acknowledged that biotechnology-derived proteins may mediate *in vivo* effects that cannot be fully  
151 elucidated by *in vitro* studies. Therefore, non-clinical evaluation in *in vivo* studies may be necessary to  
152 provide complementary information, provided that a relevant *in vivo* model with regard to species or  
153 design is available.

154 Factors to be considered when the need for *in vivo* non-clinical studies is evaluated, include, but are  
155 not restricted to:

- 156 • Presence of relevant quality attributes that have not been detected in the reference product (e.g.  
157 new post-translational modification structures).
- 158 • Significant quantitative differences in quality attributes between the intended biosimilar and the

159 reference product.

- 160 • Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-  
161 derived proteins.

162 Although each of the factors mentioned above do not necessarily warrant *in vivo* testing, these issues  
163 should be considered together to assess the level of concern and whether there is a need for *in vivo*  
164 testing.

165 If the comparability exercise in the *in vitro* studies in step 1 is considered satisfactory and no factors of  
166 concern are identified in step 2, or these factors do not block direct entrance into humans, an *in vivo*  
167 animal study may not be considered necessary.

168 If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot  
169 sufficiently be characterised on a quality and *in vitro* level, *in vivo* studies may be necessary.  
170 Applicants should then carefully consider if these should be performed in animals or as part of the  
171 clinical testing, e.g. in healthy volunteers.

172 If there is a need for additional *in vivo* information, the availability of a relevant animal species or  
173 other relevant models (e.g. transgenic animals, transplant models) should be considered.

174 If a relevant *in vivo* animal model is not available the applicant may choose to proceed to human  
175 studies taking into account principles to mitigate any potential risk.

### 176 **4.3. Step 3: *In vivo* studies**

177 If an *in vivo* evaluation is deemed necessary, the focus of the study/studies (PK and/or PD and/or  
178 safety) depends on the need for additional information. Animal studies should be designed to maximise  
179 the information obtained. The principles of the 3Rs (replacement, refinement, reduction) should be  
180 considered when designing any *in vivo* study. Depending on the endpoints needed, it may not be  
181 necessary to sacrifice the animals at the end of the study. The duration of the study (including  
182 observation period) should be justified, taking into consideration the PK behaviour of the  
183 biotechnology-derived product and its clinical use.

184 When the model allows, the PK and PD of the biosimilar and the reference medicinal product should be  
185 quantitatively compared, including concentration-response assessment covering the therapeutic dose  
186 range in humans.

187 For safety studies a flexible approach should be considered, in particular if non-human primates are  
188 the only relevant species. The conduct of standard repeated dose toxicity studies in non-human  
189 primates is usually not recommended. If appropriately justified, a repeated dose toxicity study with  
190 refined design (e.g. using just one dose level of biosimilar and reference product and/or just one  
191 gender and/or no recovery animals) or an in-life evaluation of safety parameters (such as clinical  
192 signs, body weight and vital functions) may be considered.

193 The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on  
194 impurities) is not recommended. Due to the different production processes used by the biosimilar and  
195 reference product manufacturers, qualitative differences of process related impurities will occur (e.g.  
196 host cell proteins). The level of such impurities should be kept to a minimum, which is the best  
197 strategy to minimise any associated risk.

198 Qualitative or quantitative difference(s) of product-related variants (e.g. glycosylation patterns, charge  
199 variants) may affect biological functions of the biotechnology-derived protein and are expected to be  
200 evaluated by appropriate *in vitro* assays. These quality differences may have an effect on immunogenic

201 potential and the potential to cause hypersensitivity. It is acknowledged that these effects are difficult  
202 to predict from animal studies and should be further assessed in clinical studies.

203 Although immunogenicity assessment in animals is generally not predictive for immunogenicity in  
204 humans, it may be needed for interpretation of *in vivo* studies in animals. Therefore, blood samples  
205 should be taken and stored for future evaluations if then needed.

206 Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required  
207 for non-clinical testing of biosimilars.

208 Studies on local tolerance are usually not required. However, if excipients are introduced for which  
209 there is no or little experience with the intended clinical route, local tolerance may need to be  
210 evaluated. If other *in vivo* studies are performed, evaluation of local tolerance may be part of the  
211 design of that study instead of the performance of separate local tolerance studies.

## 212 **5. Clinical studies**

213 It is acknowledged that the manufacturing process of the biosimilar product will be optimised during  
214 development. However, it is recommended to generate the clinical data required for the comparability  
215 study with the test product derived from the final manufacturing process and therefore representing  
216 the quality profile of the batches to become commercialised. Any deviation from this recommendation  
217 should be justified and supported by adequate additional bridging data.

218 The clinical comparability exercise is normally a stepwise procedure that should begin with  
219 pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and  
220 safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical  
221 comparability.

### 222 **5.1. Pharmacokinetic studies**

223 Comparative PK studies designed to demonstrate similar PK profile of the biosimilar and the reference  
224 medicinal product with regard to key PK parameters are an essential part of the biosimilar  
225 development programme.

226 The design of the study depends on various factors, including clinical context, safety, PK characteristics  
227 of the reference product (target-mediated disposition, linear or non-linear PK, time-dependency, half-  
228 life, etc.) as outlined in the *Guideline on the clinical investigation of the pharmacokinetics of*  
229 *therapeutic proteins* (CHMP/EWP/89249/2004) and, as applicable, the *Guideline on the investigation of*  
230 *bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Furthermore, bioanalytical assays should be  
231 appropriate for their intended use and adequately validated as outlined in the *Guideline on*  
232 *bioanalytical method validation* (EMA/CHMP/EWP/192217/2009).

233 The criteria used in standard clinical bioequivalence studies, initially developed for chemically derived,  
234 orally administered products may be acceptable in the absence of specific criteria for biologicals.  
235 Nevertheless, the comparability limits for the main PK parameters should be defined and justified prior  
236 to conducting the study.

237 For the demonstration of comparable pharmacokinetics, it is advisable to select the most sensitive test  
238 model. Healthy volunteers lack co-morbidity and co-medications and are likely to have less target-  
239 mediated clearance compared to patients. A single dose cross-over study with full characterisation of  
240 the PK profile, including the late elimination phase, is preferable. A parallel group design may be  
241 necessary with substances with a long half life and high risk of immunogenicity.



242 PK studies are not always possible or feasible in healthy volunteers. In this case, the PK needs to be  
243 studied in patients. The most sensitive model/population, i.e. that has fewer factors that cause major  
244 inter-individual or time-dependent variation, should be explored.

245 In certain cases, such as important target-mediated clearance, highly immunogenic proteins or highly  
246 variable PK parameters, it may be useful to collect additional PK data within the confirmatory efficacy  
247 clinical trial(s) as it allows further investigation of the clinical impact of variable pharmacokinetics and  
248 possible changes in the PK over time. This can be achieved by determining the PK profile in a subset of  
249 patients or by population pharmacokinetics. Anti-drug antibodies should be measured in parallel to PK  
250 assessment using the most appropriate sampling time points.

251 If the reference product can be administered both intravenously and subcutaneously, the evaluation of  
252 subcutaneous administration will usually be sufficient as it covers both absorption and elimination.  
253 Thus, it is possible to waive the evaluation of intravenous administration if comparability in both  
254 absorption and elimination has been demonstrated for the subcutaneous route

255 In a single dose PK study, the primary parameters are the  $AUC_{(0-\text{inf})}$  for i.v. administration and  $AUC_{(0-\text{inf})}$   
256 and usually  $C_{\text{max}}$  for subcutaneous administration. Secondary parameters such as  $t_{\text{max}}$ , volume of  
257 distribution, and half-life, should also be estimated. In a multiple dose study, the primary parameters  
258 should be the truncated AUC after the first administration until the second administration ( $AUC_{0-t}$ ) and  
259 AUC over a dosage interval at steady state ( $AUC_{\tau}$ ). Secondary parameters are  $C_{\text{max}}$  and  $C_{\text{trough}}$  at  
260 steady state.

## 261 **5.2. Pharmacodynamic studies**

262 It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies  
263 whenever feasible. The PD markers should be selected on the basis of their clinical relevance.

264 Normally, comparative efficacy trials are required for the demonstration of clinical comparability. In  
265 certain cases, however, comparative PK/PD studies between the test and the reference medicinal  
266 product may be sufficient to demonstrate clinical comparability, provided that all the following  
267 conditions are met:

- 268 • A clear dose-response relationship has been demonstrated. If not, the recommended study design  
269 is to conduct a multiple dose-exposure-response study. This design would ensure that the  
270 biosimilar and the reference can be compared within the linear ascending part of the dose response  
271 curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be  
272 sensitive but it cannot replace dose comparative studies.
- 273 • The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient  
274 outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar  
275 effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the  
276 effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic  
277 hepatitis C to assess the effect of alpha interferons, euglycaemic clamp test to compare two  
278 insulins, and magnetic resonance imaging of disease lesions to compare two  $\beta$ -interferons.

279 The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of  
280 surrogacy is very rare. In such cases, a combination of markers selected based on sound  
281 pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to  
282 conclude on clinical comparability.



283 When evidence to establish clinical comparability will be derived from studies with PD  
284 markers/biomarkers, it is recommended to discuss such approach with regulatory authorities. This  
285 should include a proposal of the size of the proposed equivalence margin and its clinical justification.

### 286 **5.3. Efficacy trials**

287 Usually, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference  
288 medicinal product in adequately powered, randomised, parallel group comparative clinical trial(s),  
289 preferably double-blind. The study population should be representative of approved therapeutic  
290 indication(s) of the reference product and be sensitive for detecting potential differences between the  
291 biosimilar and the reference. Occasionally, changes in the clinical praxis mandate a deviation from the  
292 approved therapeutic indication, e.g. in terms of concomitant medication used as combination  
293 treatment, line of therapy, or severity of the disease. Deviations need to be justified and discussed  
294 with regulatory authorities.

#### 295 **5.3.1. Study designs**

296 In general, an equivalence design should be used. The use of a non-inferiority design may be  
297 acceptable if justified on the basis of a strong scientific rationale and taking into consideration the  
298 characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response  
299 relationship. A non-inferiority trial may only be accepted where the possibility of increased efficacy can  
300 be excluded on scientific and mechanistic grounds. However, as in equivalence trials assay sensitivity  
301 has to be considered.

302 It is recommended to discuss the use of a non-inferiority design with regulatory authorities.

#### 303 **5.3.2. Efficacy endpoints**

304 Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy per se, since this  
305 has already been established with the reference product. The sole purpose of the efficacy trials is to  
306 investigate whether a clinically significant difference between the reference and biosimilar products can  
307 be detected.

308 CHMP has issued disease-specific guidelines for development of innovative medicinal products. In the  
309 development of a biosimilar medicinal product, the choice of clinical endpoints and time points of  
310 analysis of endpoints may deviate from the guidance for new active substances. Therefore, CHMP has  
311 issued product-class-specific guidelines to guide the development of biosimilar medicinal products in  
312 certain areas. In the absence of such a guideline, the applicant should select the most sensitive  
313 endpoints. Nevertheless, deviations from disease-specific guidelines need to be scientifically justified.  
314 Differences detected should always be discussed as to whether they are clinically relevant.

315 The correlation between the "hard" clinical endpoints recommended by the guidelines for new active  
316 substances and other clinical/pharmacodynamic endpoints that are sensitive to detect differences may  
317 have been demonstrated in clinical trials with the reference product. In this case, it is not necessary to  
318 use the same primary efficacy endpoints as those that were used in the marketing authorisation  
319 application of the reference product. However, it is advisable to include some common endpoints (e.g.  
320 as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference  
321 product.

322 Clinical comparability margins should be pre-specified and justified on both statistical and clinical  
323 grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical

324 trials and CHMP [guideline CPMP/EWP/2158/99 on the choice of the non-inferiority margin](#). As for all  
325 clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered.

#### 326 **5.4. Clinical safety**

327 Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety  
328 profile. Clinical safety is important throughout the clinical development programme and is captured  
329 during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study establishing  
330 comparability. Comparative safety data should normally be collected pre-authorisation, their amount  
331 depending on the type and severity of safety issues related to the reference product. The duration of  
332 safety follow-up pre authorisation should be justified. Care should be given to compare the type,  
333 severity and frequency of the adverse reactions between the biosimilar and the reference product,  
334 particularly those described in the SmPC of the reference product. The applicant should provide in the  
335 application dossier an evaluation of the specific risks anticipated for the biosimilar. This includes in  
336 particular a description of possible safety concerns related to infusion-related reactions and  
337 immunogenicity of the biosimilar that may result from a manufacturing process different from that of  
338 the reference product.

339 The principles for the assessment of immunogenicity of therapeutic proteins have been described in  
340 two CHMP guidelines (EMA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010). The potential  
341 for immunogenicity of a biosimilar should always be investigated in a comparable manner to the  
342 reference product and should follow the principles as laid down in the aforementioned CHMP guidelines  
343 unless it can be justified that there is a need for deviation from this approach. The amount of  
344 immunogenicity data will depend on the reference product and/or the product class.

345 Immunogenicity testing of the biosimilar and the reference products should be conducted within the  
346 comparability exercise by using the same assay format and sampling schedule. Assays should be  
347 performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure  
348 the immune response against the product that was received by each patient. Usually the incidence of  
349 antibodies and antibody titres should be measured and presented. Duration of the immunogenicity  
350 study should be justified on a case-by-case basis depending on the duration of the treatment course,  
351 disappearance of the product from the circulation (to avoid antigen interference in the assays) and the  
352 time for emergence of humoral immune response (at least four weeks in case of an  
353 immunosuppressive agent). Duration of follow-up should be justified based on the time course and  
354 characteristics of unwanted immune responses described for the reference medicinal product, e.g. a  
355 low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity  
356 over time. In case of chronic administration, one-year follow up data will normally be required pre-  
357 licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified based on the  
358 immunogenicity profile of the reference product. Immunogenicity data for the additional period, up to  
359 one-year, could then be submitted post-authorisation.

360 A higher immunogenicity as compared to the reference product may become an issue for the  
361 benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the  
362 biosimilar is also possible scenario, which would not preclude approval as a biosimilar. In case of  
363 reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire  
364 study population could erroneously suggest that the biosimilar is more efficacious than the reference  
365 product. It is therefore recommended to pre-specify an additional exploratory subgroup analysis of  
366 efficacy and safety in those patients that did not mount an anti-drug antibody response during the  
367 clinical trial. This subgroup analysis could be helpful to establish that the efficacy of the biosimilar and  
368 the reference product are in principle similar if not impacted by an immune response.

369 For biologicals with multiple indications, immunogenicity could differ among indications and absence of  
370 immunogenicity assessment in a particular indication for the biosimilar may have to be justified.

## 371 **6. Extrapolation of efficacy and safety from one therapeutic** 372 **indication to another**

373 In case the reference medicinal product has more than one therapeutic indication, the efficacy and  
374 safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the  
375 claimed indications. Justification will depend on, e.g., clinical experience, available literature data,  
376 mechanisms of action of the active substance of the reference product in each indication (including its  
377 degree of certainty), and on receptors involved. Binding of the reference substance to the same  
378 receptors may have different effects in different target cells depending on differences in the  
379 intracellular signalling pathways, e.g. due to transformation. This situation is not an argument for  
380 additional studies. However, if there is evidence that different active sites of the reference product or  
381 different receptors of the target cells are involved in different therapeutic indications or that the safety  
382 profile of the product differs between the therapeutic indications, additional data may be needed to  
383 justify the extrapolation of safety and efficacy from the indication studied in the pivotal clinical trial.  
384 For the extrapolation of safety, the Applicant should consider patient-related factors, such as different  
385 co-medication, co-morbidities, and immunological status, and disease-related factors, such as  
386 reactions related to the target cells, e.g. lysis of tumour cells. The extent of such data should be  
387 considered in the light of the totality of evidence derived from the biosimilar comparability exercise and  
388 the potential remaining uncertainties.

## 389 **7. Pharmacovigilance**

390 Data from pre-authorisation clinical studies are usually insufficient to identify rare adverse effects.  
391 Therefore, clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-  
392 approval phase including continued benefit-risk assessment.

393 Within the authorisation procedure the applicant should present a description of the pharmacovigilance  
394 system and a risk management plan in accordance with current EU legislation and pharmacovigilance  
395 guidelines. The risk management plan should take into account identified and potential risks associated  
396 with the use of the reference product and, if applicable, additional potential risks identified during the  
397 development programme of the biosimilar and should detail how these issues will be addressed in  
398 post-marketing follow-up. Immunogenicity should specifically be addressed in this context. Within the  
399 pharmacovigilance plan, any specific safety monitoring imposed on the reference medicinal product or  
400 product class should be taken into consideration. Applicants are encouraged to participate in already  
401 existing pharmacoepidemiological studies in place for the reference product. Risk minimisation  
402 activities in place for the reference medicinal product should also be included into the risk management  
403 programme of the biosimilar.

404 For suspected adverse reactions relating to biological medicinal products, the definite identification of  
405 the concerned product with regard to its manufacturing is of particular importance. Therefore, all  
406 appropriate measures should be taken to identify clearly any biological medicinal product which is the  
407 subject of a suspected adverse reaction report, with due regard to the name of the medicinal product  
408 and the batch number.

409 Depending on the handling of biosimilars and reference medicinal products in clinical practice at  
410 national level, 'switching' and 'interchanging' of medicines that contain a given biological might occur.  
411 Thus, applicants are recommended to follow further development in the field and consider these

412 aspects as part of the risk management plan. In addition, available data on switching should be  
413 carefully assessed during the review of adverse reaction reports.

