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4 **Guideline on similar biological medicinal products**
5 **containing monoclonal antibodies**
6 **Draft**

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11 Guideline on Similar Biological Medicinal Products
12 Containing Monoclonal Antibodies

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38 **Executive summary**

39 This guideline lays down the non-clinical and clinical requirements for monoclonal antibody (mAb)
40 containing medicinal products claiming to be similar to another one already marketed. The non-clinical
41 section addresses the pharmaco-toxicological requirements and the clinical section the requirements
42 for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance
43 aspects.

44 As regards non-clinical development, a risk-based approach to evaluate mAb on a case-by-case basis
45 is recommended to decide on the choice and extent of *in vitro* and *in vivo* studies. *In vitro* studies
46 should be conducted first, and a decision then made as to the extent of what, if any, *in vivo* work will
47 be required. If an *in vivo* study is deemed necessary, the focus of the study (pharmacokinetics,
48 pharmacodynamics, and/or safety; normally comparative in nature) depends on the need for additional
49 information, and the availability of a relevant animal model. The conduct of large comparative
50 toxicological studies in non-human primates is not recommended. As regards clinical development, a
51 comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population
52 (healthy volunteers or patients) normally forms an integral part of biosimilar mAb development,
53 usually in a parallel group design due to the long half-life of mAbs and potential interference of
54 immunogenicity. The design of a pharmacokinetic study will depend on various factors, including
55 clinical context, linear versus non-linear pharmacokinetics etc. Pharmacokinetic data can be helpful to
56 extrapolate data on efficacy and safety between different clinical indications of the reference mAb. It
57 may, on a case-by-case basis, be necessary to undertake multidose pharmacokinetic studies in
58 patients, or even to perform pharmacokinetic assessment as part of the clinical study designed to
59 establish similar efficacy and safety. Pharmacokinetic studies can be combined with pharmacodynamic
60 (PD) endpoints, where available. Sponsors should always explore possibilities to study dose-
61 concentration-response relationships since this approach, if successful, may provide strong evidence of
62 biosimilarity. Normally, similar clinical efficacy should be demonstrated in adequately powered,
63 randomised, parallel group comparative clinical trial(s), preferably double-blind, normally equivalence
64 trials. To establish biosimilarity, deviations from disease-specific guidelines issued by the CHMP (for
65 example, choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy,
66 etc) may be warranted. The focus of the biosimilarity exercise is to demonstrate similar efficacy and
67 safety compared to the reference product, not patient benefit per se, which has already been shown
68 for the reference product. In principle, the most sensitive model and study conditions
69 (pharmacodynamic or clinical) should be used in a homogeneous patient population, since this reduces
70 variability and thus the sample size needed to prove similarity, and can simplify interpretation. In
71 cases where comparative pharmacodynamic studies are claimed to be most suitable to provide the
72 pivotal evidence for similar efficacy, Applicants will have to choose clinically relevant markers and also
73 provide sufficient reassurance of clinical safety, particularly immunogenicity. It may be difficult to
74 define an appropriate equivalence margin for pharmacodynamic equivalence based on clinical
75 relevance, and to provide reassurance that all relevant aspects of a biosimilar mAb as regards similar
76 clinical efficacy are covered. Comparable safety with respect to pharmacologically mediated adverse
77 reactions could also be considered as a measure of biosimilarity. Extrapolation of clinical efficacy and
78 safety data to other indications of the reference mAb, not specifically studied during the clinical
79 development of the biosimilar mAb, is possible based on the results of the overall evidence provided
80 from the biosimilarity exercise and with adequate justification. As regards post-authorisation follow-up,
81 the concept to be proposed by Applicants may have to exceed routine pharmacovigilance, and may
82 have to involve more standardized environments.

83 **1. Introduction**

84 Monoclonal antibodies have been established as a major product class of biotechnology-derived
85 medicinal products. Different mAb products share some properties, e.g. being cytotoxic to their target,
86 or neutralizing a cytokine, but differ in aspects like the mechanism of action. On one hand, they are
87 structurally complex, and may have several functional domains within a single molecule, depending on
88 the isotype (antigen-binding region, complement-binding region, constant part interacting with Fc
89 receptors). Each individual mAb may present a unique profile with respect to the criticality of the
90 antigen-binding region, the Fc cytotoxic effector function, and binding to Fc receptors including FcRn.
91 On the other hand, various assays have been established in the past years that allow for more in-depth
92 characterisation of complex proteins, both on a physicochemical and a functional level, e.g. with
93 potency assays. However, it may at the current stage of knowledge be difficult to conclude on the
94 relevance of minor quality differences in the physicochemical and biological characterization.
95 Nevertheless, such mAbs are being developed, and CHMP has given scientific advice for the
96 development of some individual products. This guideline lays down the non-clinical and clinical
97 requirements for monoclonal antibody-containing medicinal products claiming to be similar to another
98 one already marketed, i.e. similar biological medicinal products (biosimilars).

99 For quality aspects the principles as laid out in the comparability guidelines including the "Guideline on
100 similar biological medicinal products containing biotechnology-derived proteins as active substance:
101 Quality issues" (EMA/CHMP/ 49348/05) and the "Guideline on production and quality control of
102 monoclonal antibodies and related substances" (CHMP/BWP/157653/07) apply. Although specific
103 considerations as regards quality of biosimilar mAbs are important, these are relevant in a more
104 general context and will thus be implemented in a revision of the Guideline EMA/CHMP/49348/05 (see
105 concept paper published at EMA website).

106 **2. Scope**

107 The "Guideline on similar biological medicinal products containing biotechnology-derived proteins as
108 active substance: non-clinical and clinical issues" (EMA/CPMP/42832/05/) lays down the general
109 requirements for demonstration of the similar nature of two biological products in terms of safety and
110 efficacy. This product specific guidance complements the above guideline and presents the current
111 view of the CHMP on the application of the guideline for demonstration of biosimilarity of two mAb-
112 containing medicinal products. While this guidance is specifically related to mAbs, the principles
113 discussed may also, on a case-by-case basis, be relevant for related substances like for example fusion
114 proteins based on IgG Fc (-cept molecules).

115 Second- or next-generation biologicals, defined as biologicals that are structurally and/or functionally
116 altered, in comparison to already licensed reference products, to gain an improved or different clinical
117 performance, are beyond the scope of this guideline. Nevertheless, principles laid down in this
118 guideline could apply on a case-by-case basis. In these cases Sponsors are recommended to seek
119 scientific advice from the European Medicines Agency, or from national competent authorities.

120 **3. Legal basis**

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

123

124 **4. Non-clinical studies**

125 A risk-based approach to evaluate mAb on a case-by-case basis is recommended.

126 Non-clinical studies should be performed before initiating clinical development. *In vitro* studies should
127 be conducted first and a decision then made as to the extent of what, if any, *in vivo* work will be
128 required.

129 The approach taken will need to be fully justified in the non-clinical overview.

130 **4.1. *In vitro* pharmacodynamic (PD) studies = step1**

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

134 *In vitro* non-clinical studies should include relevant studies on:

- 135 • Binding to the target antigen
- 136 • Binding to all Fcγ receptors, FcRn and complement
- 137 • Fab-associated functions (e.g. neutralization, receptor activation or receptor blockade)
- 138 • Fc-associated functions (ADCC and CDC assays, complement activation)

139 These concentration/activity studies should be comparative in nature and should be designed to
140 exclude all differences of importance in the concentration – activity relationship between the similar
141 biological medicinal product and the reference medicinal product and should not just assess the
142 response per se.

143 Together these assays should cover all functional aspects of the mAb even though some may not be
144 considered necessary for the mode of action in the clinic. As these assays may be more specific and
145 sensitive than studies in animals, these assays can be considered fundamental in the non-clinical
146 comparability exercise. It is acknowledged, however, that some mAbs may mediate effects *in vivo* in
147 ways that are not yet fully elucidated.

148 **4.2. Identification of factors of importance for the *in vivo* non-clinical** 149 **strategy = step 2**

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

- 152 • Differences in process-related impurities due to a different cell expression system compared with
153 the reference medicinal product (e.g. yeast, insect, plant, vs. mammalian expression system).
- 154 • The presence of a mixture of product- and/or process related impurities that can be less well
155 characterized.
- 156 • Significant differences in formulation, use of not widely used excipients.
- 157 • The need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in
158 healthy volunteers
- 159 • Availability of a relevant *in-vivo* model (with regard to species or design, e.g. transplantation
160 models) which is likely capable of providing interpretable data on similar *in vivo* behaviour of
161 biosimilar and reference mAb.

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

164 **4.3. *In vivo* studies = step 3**

165 If the comparability exercise in the *in vitro* PD studies in step 1 is considered satisfactory and no
166 factors of concern are identified in step 2, an *in vivo* animal study is not considered necessary.

167 If the outcome of steps 1 and 2 raises concerns, the need for comparative *in vivo* studies should be
168 decided case-by-case.

169 If an *in vivo* study is deemed necessary, the focus of the study (PK, PD and/or safety) depends on the
170 need for additional information. Animal studies should be designed to maximise the information
171 obtained, and safety and PD endpoints may be included in a PK study if considered appropriate and
172 feasible.

173 The possibility of performing *in vivo* comparative PK and PD studies depends on the characteristics of
174 the product, and on the availability of a relevant animal species, or other relevant models (e.g.
175 transgenic animals or transplant models) and their sensitivity. Such model would have to allow for
176 quantitative comparison of PK and PD of the similar biological medicinal product and the reference
177 medicinal product, including dose-response assessment covering a therapeutic dose in humans.

178 Due to the specificity of mAbs, the relevant species for toxicology studies is in most cases a non-
179 human primate. The conduct of large comparative toxicological studies in non-human primates is not
180 recommended. If safety testing *in vivo* is needed in non-human primates, the use of only one dose and
181 one gender and omission of a recovery group might be justified. In principle, the toxicology study
182 should be comparative in nature, unless scientific justification can be provided to indicate that a direct
183 comparison is unnecessary. The duration of the study should be justified, taking into consideration the
184 PK behaviour of the mAb and the clinical posology.

185 The conduct of toxicity studies in non-relevant species (i.e. only to assess unspecific toxicity, based on
186 impurities) is not recommended.

187 Immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, but
188 may be needed for interpretation of PK studies and toxicity findings (or lack thereof). Blood samples
189 should be taken and stored for future evaluations if then needed.

190 Local tolerance endpoints should only be included in an *in vivo* study if there is a special need for
191 additional information.

192 Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine
193 requirements for non-clinical testing of similar biological medicinal products containing monoclonal
194 antibodies as active substance.

195 **5. Clinical Studies**

196 **5.1. Pharmacokinetics (PK)**

197 **5.1.1. Study design**

198 The comparison of the pharmacokinetic properties of the similar biological medicinal product and the
199 reference product form an integral part of biosimilar mAb development. A parallel group design is
200 acceptable due to the long half-life of monoclonal antibodies and the potential influence of
201 immunogenicity. Clearance may change significantly after a first dose, hence therapeutic response and

202 severity of the disease can affect PK. In such cases, in principle, a single dose PK evaluation is most
203 sensitive. However, for the design of a PK study for a biosimilar mAb, particulars like the clinical
204 context will have to be taken into account. The design of the study depends on the PK characteristics
205 of the antibody (linear or non-linear PK, time-dependencies) and should take into account the
206 recommendations as outlined in the "Guideline on the clinical investigation of the pharmacokinetics of
207 therapeutic proteins" (CHMP/EWP/89249/2004).

208 **5.1.2. Selection of a sensitive population**

209 The primary objective of the pharmacokinetic studies performed to support a Marketing Authorisation
210 Application (MAA) for a similar biological medicinal product is to show comparability in
211 pharmacokinetics of the biosimilar with the reference product in a sufficiently sensitive and
212 homogeneous population. Choice of a homogeneous population is expected to reduce variability and
213 thus the sample size needed to prove equivalence, and can simplify interpretation.

214 Single dose studies may be possible in healthy volunteers with adequate justification, depending on
215 the mAb. For mAbs licensed in several clinical indications, it is not generally required to investigate the
216 pharmacokinetic profile in all of them. However, if distinct therapeutic areas are involved for one
217 particular mAb (e.g. autoimmunity and oncology), separate PK studies may be recommendable as a
218 support for extrapolation between these indications. Applicants should focus on the patient population
219 where pharmacokinetic equivalence to the reference mAb can be studied with sufficient sensitivity. The
220 choice of the patient population should be fully justified, based on a comprehensive survey of scientific
221 literature, as regards sensitivity, and also the possibility to infer PK results to the other clinical
222 indications where the reference mAb is licensed. Factors that may influence the choice of the patient
223 population are age of usual manifestation and age range (since lower age may be less prone to
224 presence of concomitant clinical conditions), number of previous treatments, concomitant treatments,
225 or expression of antigen (which may be related to disease stage). Another factor is the dosage regimen
226 in different populations: In case of nonlinear PK with overproportional increase, a comparison in the
227 population with the highest dosage regimen would be advisable.

228 It may be necessary to perform the PK study in a different patient population than the clinical trial
229 designed to establish similar clinical efficacy, since the population where PK is measured most
230 sensitively may not be the same as the population where similar efficacy and safety can be measured
231 most sensitively. In such scenarios, population PK measurements of sampling during the phase III
232 study are recommended as additional information, since such data may add relevant data to the
233 overall database to claim biosimilarity, and may support extrapolation between indications.

234 **5.1.3. Multidose PK and endpoints**

235 If a multidose PK study in patients is performed, sampling should normally be undertaken after the
236 first dose and later, preferably at steady state. The preferred PK endpoints may depend on the type of
237 mAb and on the known PK characteristics (linear or non-linear PK). Usually employed primary
238 parameters are AUC, C_{max}, and C_{trough} in determinations at steady state. Other PK parameters like
239 clearance and half-life should be determined and reported in a descriptive manner. If relevant
240 differences occur the assumption of similar PK might be seriously questioned. If such results are
241 observed, it is recommended to consult regulatory authorities on the further proceeding of a biosimilar
242 mAb development.

243 PK investigations both after the first dose and at a later dose interval (steady state) should be
244 considered in light of the long loading dose interval and long half-life of mAbs and, especially in case of
245 nonlinear PK of the reference mAb. In such case (e.g. many cytotoxic mAbs with cellular targets),
246 clearance and half-life are concentration (dose) dependent. This dependency has impact on steady

247 state levels. In these cases PK comparison of steady state levels after multiple dosing are considered
248 most appropriate (AUC_{SS} , $C_{max,SS}$, $C_{trough,SS}$). Concentration-, time-dependent or immunogenicity-
249 related changes in distribution or elimination kinetics may occur leading to differences in PK after
250 repeat administration. Thus, anti-drug antibodies should be measured in parallel.

251 Equivalence margins have to be defined a priori and appropriately justified. For some mAbs, inter-
252 subject variability for some parameters was reported to be considerable. This may have to be
253 accounted for in the choice of the equivalence margin at least for such parameters. As a principle, any
254 widening of the conventional equivalence margin beyond 80-125% requires thorough justification,
255 including an estimation of potential impact on clinical efficacy and safety. This should be discussed with
256 regulatory authorities. Of note, these studies are undertaken with the aim to exclude differences in the
257 PK behaviour of the biosimilar. A significant difference, yet fulfilling equivalence criteria, may indicate
258 potential differences in the interaction between the target antigen(s) and the biosimilar mAb, and thus
259 may question the biosimilarity concept.

260 Usually, proof of similar PK profiles should precede clinical trials. However, in certain scenarios, e.g. for
261 mAbs where PK is inevitably highly variable even within one clinical indication, it may, for feasibility
262 reasons, be necessary to explore PK comparisons as part of a clinical study that is designed to
263 establish similar clinical efficacy (as only this trial will then be large enough to demonstrate PK
264 equivalence). In this case an exploratory PK study with the objective of investigating tolerability and
265 obtaining an initial trend for evidence of pharmacokinetic equivalence applying a preliminary and less
266 stringent equivalence requirement as a stop/go indicator before commencing the comparative clinical
267 efficacy trial should normally be performed. To start with a comparative clinical efficacy trial that
268 includes PK, without formal phase I study, could also become problematic, as there was no former
269 exposure of humans to the biosimilar mAb, together with potentially limited non-clinical data,
270 depending on the mAb. If the PK and PD biosimilarity exercise is to be included into the clinical efficacy
271 trial, proper measures have to be pre-planned to ensure the statistical rigour and integrity of this trial.
272 It is recommended that such concepts are discussed with regulatory authorities before commencing
273 such a trial. It will be necessary to consider the objective of the interim analysis on PK parameters (to
274 exclude large differences in PK such that it would be unsafe or unethical to continue the study, or to
275 establish PK equivalence), access to unblinded PK data, which usually need not include sponsor
276 personnel or trial investigators, and whether design modifications might be envisaged (including
277 additional interim analyses). A design in which PK data are analysed and interpreted by an
278 independent monitoring committee without treatment allocation being revealed to sponsors and
279 investigators could be accepted.

280 **5.1.4. Additional considerations for PK measurements of cytotoxic mAbs in** 281 **anticancer indications**

282 Pharmacokinetics of anticancer (cytotoxic) mAbs may be time dependent, as the tumour burden may
283 change after multiple dosing (in case of response increase of half-life with multiple dosing). This should
284 be taken into account in the design of the study and statistical analyses. For mAb targets that involve
285 receptor shedding, it is advisable to measure shed receptor levels at baseline and, if relevant, during
286 the conduct of the study, in order to verify the baseline comparability of the treatment groups and to
287 generate helpful additional data. An exploratory statistical analysis, if possible, on post-baseline
288 comparability at the timepoint relevant to the conclusion of PK equivalence could be helpful.

289 When several therapeutic regimens are licensed for a reference mAb, the comparative pharmacokinetic
290 study between biosimilar and reference mAb should be designed to demonstrate clinical comparability
291 selecting the most sensitive key PK parameters. Subject to reasonable justification, there is no need to
292 test all therapeutic dose regimens. Similar considerations apply for mAbs which are indicated for both,

293 monotherapy and in combination with chemotherapy. It is usually recommended to study the
294 comparative PK in the monotherapy setting in order to minimize sources for variability, although
295 chemotherapy often does not significantly alter PK characteristics.

296 With regard to the “model” indication for a comparative PK study, an adjuvant setting in patients with
297 early cancer, if possible, may be advisable, since the tumour burden is low. However, clearance due to
298 mAb-antigen interaction will not be captured. Thus, the choice of the population should be justified
299 accordingly.

300 **5.2. Pharmacodynamics (PD)**

301 Pharmacokinetic studies can be combined with pharmacodynamic (PD) endpoints, where available.
302 With regard to pharmacodynamic evaluation, there is often a lack of specific PD endpoints. Therefore,
303 the emphasis will often be on non-clinical PD evaluations, e.g. *in-vitro* testing.

304 Sponsors should always explore possibilities to study dose-concentration-response relationships since
305 this approach, if successful, may provide strong evidence of biosimilarity. A single or repeat dose study
306 in the saturation part of the dose-concentration-response curve is unlikely to discriminate between
307 different activities, should they exist. Thus, PD data from lower dose(s) may, in principle, provide
308 already pivotal information for the biosimilarity exercise. It is acknowledged that dose-response data
309 may not exist for the reference mAb, and that exposing patients to a relatively low dose of the mAbs,
310 in a worst case scenario, might sensitize them to develop anti-mAb antibodies, and, consequently, may
311 make them treatment resistant. However, for some reference mAbs clinical conditions may exist where
312 such studies are feasible. It may be more challenging to define an appropriate equivalence margin for
313 establishing equivalent efficacy based on PD markers than on clinical endpoints. Applicants will have to
314 provide reassurance that all relevant aspects of a biosimilar mAb as regards similar clinical efficacy are
315 covered. In particular, where different mechanisms of action are relevant for the claimed indication(s)
316 of the reference product, or uncertainty exists, Applicants should provide relevant data to cover
317 pharmacodynamics for all claimed clinical indications. In such cases, the sponsor should seek for
318 scientific advice for study design and duration, choice of doses, efficacy / pharmacodynamic
319 endpoints and their relevance as regards clinical meaningfulness, and comparability margins.

320 **5.3. Clinical Efficacy**

321 If dose comparative and highly sensitive PD studies cannot be performed convincingly showing
322 comparability in a clinically relevant manner, similar clinical efficacy between the similar and the
323 reference product should be demonstrated in adequately powered, randomised, parallel group
324 comparative clinical trial(s), preferably double-blinded and normally equivalence trials.

325 With regard to the specific issues with equivalence trials, e.g. assay sensitivity, reference is made to
326 guideline ICH E10 and the “Guideline on the choice of the non-inferiority margin”. For most of the
327 clinical conditions that are licensed for mAbs, specific CHMP guidance on the clinical requirements
328 exists. However, to establish biosimilarity, deviations from these guidelines (choice of endpoint,
329 timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. Such
330 deviations need to be fully scientifically justified. In such circumstances it is recommended, where
331 feasible, to include the usually recommended endpoints for a certain condition as secondary endpoint.
332 An alternative could be to provide an acceptable interim endpoint for licensing and, should the usually
333 recommended endpoint not feasibly be reached within the pivotal study, data on this endpoint could be
334 gathered in a post-authorisation setting, where feasible and considered necessary. However, such data
335 would have to be interpreted with caution, due to numerous influencing factors and likely imprecise
336 estimates.

337 Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study
338 conditions (whether licensed or not), and the applicant should justify that the model is relevant and
339 sensitive to demonstrate comparability in relation to efficacy and safety in the indication(s) applied for.
340 It is recommended that such approach is discussed upfront with regulatory authorities, e.g, via CHMP
341 Scientific Advice. In principle, the most sensitive clinical model should be used in a homogeneous
342 patient population, since this reduces the variability and thus the sample size needed to prove
343 equivalence, and can simplify interpretation. For example, patients with different disease severity and
344 with different previous lines of treatment might be expected to respond differently, and thus
345 differences between the study arms may be difficult to interpret, and it may remain uncertain whether
346 such differences would be attributable to patient or disease related factors rather than to differences
347 between the biosimilar mAb and reference mAb. The safety of patients should not be compromised by
348 a biosimilarity exercise, and patients should only be treated as medically indicated.

349 Clinical studies in special populations like the paediatric population or the elderly are normally not
350 required since the overall objective of the development programme is to establish biosimilarity, and
351 therefore the selection of the primary patient population is driven by the need for homogeneity and
352 sensitivity.

353 The inclusion of patients from non-European countries is generally possible. Knowledge of efficacy and
354 safety of the reference mAb in a particular region may be necessary in order to prospectively define an
355 equivalence margin. Stratification and appropriate subgroup analyses are normally expected if patients
356 from different global regions are included. Diagnostic and treatment strategies should be comparable
357 in order to prevent the influence of extrinsic factors.

358 **5.3.1. Additional considerations for mAbs licensed in anticancer indications**

359 Establishing similar clinical efficacy and safety of biosimilar and reference mAb may be particularly
360 challenging in an anticancer setting: According to the "Guideline on the evaluation of anticancer
361 medicinal products in man" (CHMP/EWP/205/95/Rev.3/Corr.2) the preferred endpoint to prove efficacy
362 in cancer indications would be either progression free / disease free survival (PFS / DFS) or overall
363 survival (OS). Such endpoints are important to establish patient benefit for a new anticancer drug, but
364 may not be feasible or sensitive enough for establishing biosimilarity of a biosimilar mAb to a reference
365 mAb, since they may be influenced by various factors not attributable to differences between the
366 biosimilar mAb and the reference mAb, but by factors like tumour burden, performance status,
367 previous lines of treatments, underlying clinical conditions, subsequent lines of treatment (for OS), etc.
368 They may therefore not be suitable to establish similar efficacy of the biosimilar and the reference
369 mAb.

370 The focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the
371 reference product, not patient benefit *per se*, which has already been established by the reference
372 product. Therefore, in general the most sensitive patient population and clinical endpoint is preferred
373 to be able to detect product-related differences, if present and, at the same time, to reduce patient
374 and disease-related factors to a minimum in order to increase precision. A clinical trial in a
375 homogeneous patient population with a clinical endpoint that measures activity as primary endpoint
376 may be considered. An example may be Overall Response Rate (ORR, proportion of patients in whom a
377 Complete Response (CR) or Partial Response (PR) was observed). It may also be worthwhile to explore
378 ORR measured at a certain timepoint (i.e., ORR at x months) or percentage change in tumour mass
379 from baseline instead ("waterfall plot"). Applicants should engage in efforts for a standardized
380 assessment with patients evaluated at appropriate intervals. PFS and OS should be recorded, where
381 feasible. In case PFS is likely to be more sensitive than ORR as outcome measure, this is the preferred
382 option even though this will prolong the clinical study. It is acknowledged that data on survival may

383 have to be interpreted with caution due to numerous factors influencing survival beyond the
384 performance of the biosimilar mAb or the reference mAb.
385 Novel endpoints may be employed on an exploratory basis if well justified (e.g., time to response).

386 **5.4. Clinical Safety**

387 Clinical safety is normally studied as part of the clinical study to establish similar efficacy of biosimilar
388 and reference mAb. It is recommended to use the same definitions for safety parameters as that used
389 for the reference mAbs in its original development programme (if known) where no homogeneous
390 definition exists (e.g., measurement of cardiotoxicity). Comparable safety with respect to
391 pharmacologically mediated adverse reactions (e.g., cardiotoxicity) should also be considered as a
392 measure of biosimilarity. In cases where comparative and highly sensitive PD studies are suitable to
393 provide the pivotal evidence for equivalence in clinical efficacy, Applicants will have to provide
394 sufficient reassurance of clinical safety, including immunogenicity. Prelicensing safety data should be
395 obtained in a number of patients sufficient to determine the adverse effect profiles of the biosimilar
396 medicinal product. Care should be given to compare the type, frequency and severity of the adverse
397 reactions between the similar biological medicinal product and the reference product, with focus on the
398 adverse reactions described for the reference product.

399 Rare events such as progressive multifocal leukencephalopathy are unlikely to be detected in a pre-
400 authorisation setting. Therefore, Applicants need to propose pharmacovigilance and risk management
401 activities for the post-authorisation phase at the time of the marketing authorisation application (see
402 chapter in this guideline). Usually, similar pharmacovigilance activities as those of the reference
403 product would be required, rather than a direct comparison with the reference product, since data will
404 most likely be difficult to interpret due to their rarity of occurrence.

405 When designing their development programme, sponsors should reflect upon how re-treatment of
406 patients would be handled. Concepts should be presented at the time of marketing authorisation
407 application on how to systematically measure safety of repeat exposure of patients, for example in
408 oncological indications where patients undergo several treatment cycles. It may be advisable to extend
409 the clinical study as a post-authorisation follow-up study to a full treatment cycle, where relevant and
410 feasible.

411 As regards immunogenicity assessment, Applicants should refer to existing CHMP guidance. Systematic
412 evaluation and discussion of immunogenicity is important, due to clinical consequences like loss of
413 efficacy and also likely resistance against further treatment with the reference mAb. It is recommended
414 to exclude patients previously treated with the reference mAb where possible as this could hamper
415 interpretation of the safety data and thus also decrease sensitivity for detecting differences. Study of
416 unwanted immunogenicity is especially important when a different expression system is employed for
417 the biosimilar mAb compared to the reference mAb, particularly if there is limited experience with this
418 expression system in humans. It is recommended that such approaches are discussed in advance with
419 regulatory authorities.

420 Additional long-term immunogenicity and safety data might be required post-authorisation, e.g. in
421 situations where the study duration for establishing similar clinical efficacy is rather short. As regards
422 safety across different indications licensed for the reference mAb and claimed by the biosimilar mAb, a
423 post-authorisation concept for obtaining further indication-specific safety data may be needed.

424 **6. Extrapolation of Indications**

425 Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not
426 specifically studied during the clinical development of the biosimilar mAb, is possible based on the
427 overall evidence of biosimilarity provided from the comparability exercise and with adequate
428 justification. If pivotal evidence for biosimilarity is based on PD and for the claimed indications different
429 mechanisms of action are relevant (or uncertainty exists), then Applicants should provide relevant data
430 to cover pharmacodynamics for all claimed clinical indications. Applicants should support such
431 extrapolations with a comprehensive discussion of available literature on the involved antigen
432 receptor(s), and mechanism(s) of action.

433 If a reference mAb is licensed both as an immunomodulator and as an anticancer (cytotoxic) antibody,
434 the scientific justification as regards extrapolation between the two (or more) indications is more
435 challenging. The basis for such extrapolation forms an extensive quality and non-clinical database,
436 including potency assay(s) and in-vitro assays that cover the functionality of the molecule. The
437 possibility of extrapolating safety including immunogenicity data also requires careful consideration.
438 For the mechanism of action, e.g. the depletion of immune cells, several mechanisms may play a role,
439 and at the present stage of knowledge it cannot be assumed that the same mechanisms of cell
440 depletion are of the same importance in different disease states. Antibody-dependent cytotoxicity
441 (ADCC) appears to be more important in some indications than in others. To provide further evidence
442 about the mechanism of action, it may also be helpful to perform a literature search to identify what is
443 known about potential signalling inhibition by the reference mAb that would not be covered by
444 ADCC/CDC tests, in particular direct induction of apoptosis. This could provide more knowledge on
445 potential read-outs that could be used to support biosimilarity on a molecular level.

446

447 **7. Pharmacovigilance Plan and Post-authorisation Follow-up**

448 For the marketing authorisation procedure the applicant should present a risk management
449 programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance
450 guidelines.

451 Further to safety considerations as discussed above, Applicants should provide at the time of MAA a
452 comprehensive concept how to further study safety in a post-authorisation setting including also the
453 following aspects:

- 454 • Safety in indications licensed for the reference mAb that are claimed based on extrapolation of
455 efficacy and safety data.
- 456 • Occurrence of rare and particularly serious adverse events described for the reference mAb.
- 457 • Detection of novel safety signals, as for any other biological medicinal product.

458 The concept may have to exceed routine pharmacovigilance, and may have to involve more
459 standardised environments. In addition, participation in already existing registries should be explored
460 and presented as part of the Risk Management Plan. The adequacy of such proposals will have to be
461 assessed in the context of the safety data at the time of approval, the overall data from the
462 biosimilarity exercise, and the known safety profile of the reference mAb.

463 Applicants are recommended to follow further developments in the field of handling of biosimilars and
464 reference medicinal products in clinical practice. Recommendations like recording the brand name of
465 the drugs used by physicians, could be taken into account to reinforce traceability.

466 **8. References**

- 467 Directive 2001/83/EC, as amended
- 468 Guideline on similar biological medicinal products (CHMP/437/04)
- 469 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active
470 substance: Quality issues (EMA/CHMP/BWP/49348/2005)
- 471 Guideline on production and quality control of monoclonal antibodies and related substances
472 (CHMP/BWP/157653/07)
- 473 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active
474 substance: non-clinical and clinical issues (EMA/CPMP/42832/05).
- 475 Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/ 2145/00).
- 476 Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)
- 477 Note for guidance for toxicokinetics: A guidance for assessing systemic exposure in toxicological
478 studies (CPMP/ICH/384/95)
- 479 Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins
480 (CHMP/EWP/89249/2004).
- 481 Guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95/Rev.3/Corr.2)
- 482 ICH E10 Choice of Control Group in Clinical Trials CPMP/ICH/364/96
- 483 Guideline on the choice of a non-inferiority margin CPMP/EWP/2158/99
- 484 Extrapolation of results from clinical studies conducted outside Europe to the EU-population
485 CHMP/EWP/692702/08
- 486 Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins
487 (CHMP/BMWP/14327/06)
- 488 Guideline on risk management systems for medicinal products for human use (EMA/CHMP
489 96286/2005)
- 490 Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited
491 Reporting (CPMP/ICH/377/95)
- 492 ICH Note for /guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)