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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: quality issues (revision 1)**
7 **Draft**

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9 Once finalised, this guideline will replace 'The Guideline on similar biological medicinal products
10 containing biotechnology-derived proteins as active substance: quality issues
11 (EMA/CHMP/BWP/49348/2005)'.

12
13 Comments should be provided using this [template](#). The completed comments form should be sent to
bwp.biosimilar.revision@ema.europa.eu

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36 **Executive summary**

37 The Guideline on similar biological medicinal products containing biotechnology-derived proteins as
38 active substance: quality issues lays down the quality requirements for a biological medicinal product
39 claiming to be similar to another one already marketed.

40 The guideline addresses the requirements regarding manufacturing processes, the comparability
41 exercise for quality, considering the choice of reference medicinal product, analytical methods,
42 physicochemical characterisation, biological activity, purity and quality attributes for relevant
43 specifications of the similar biological medicinal product.

44 **1. Introduction**

45 A company may choose to develop a new biological medicinal product claimed to be similar (similar
46 biological medicinal product) in terms of Quality, Safety and Efficacy to a reference medicinal product,
47 which has been granted a marketing authorisation in the Community. The development of a similar
48 biological medicinal product (biosimilar) relies in part on the scientific knowledge gained from the
49 reference medicinal product, provided that the active substance of the biosimilar has been
50 demonstrated to be similar, in physicochemical and biological terms, to the active substance of the
51 reference medicinal product.

52 Biosimilars are manufactured and controlled according to their own development, taking into account
53 relevant and up-to-date information. The product development should be performed in accordance with
54 relevant ICH and CHMP guidelines.

55 In contrast to the approach generally followed for generic medicinal products, a comparison of the
56 biosimilar to a publicly available standard is not sufficient for the purpose of comparability. The
57 biosimilar should be demonstrated to be similar to a reference medicinal product approved in the
58 Community, which is selected by the company developing the biosimilar. Consequently, an extensive
59 comparability exercise with the chosen reference medicinal product will be required to demonstrate
60 that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference
61 medicinal product.

62 It is acknowledged that the manufacturer developing a biosimilar would normally not have access to all
63 information that could allow an exhaustive comparison with the reference medicinal product,
64 particularly with regards to the manufacturing process. Nevertheless the level of detail must be such
65 that firm conclusions can be made.

66 If appropriately carried out, the comparability exercise at the quality level, including analysis of
67 relevant quality attributes with sufficiently sensitive analytical tools, could allow for the submission of a
68 Marketing Authorisation Application in accordance with Article 10(4) of Directive 2001/83/EC, as
69 amended. In such situation, the applicant would normally be required to perform relevant non-clinical
70 and clinical comparability program to complete the biosimilar development as laid down in the
71 legislation and technical guidelines.

72 **2. Scope**

73 This guideline addresses quality aspects of the demonstration of comparability for similar biological
74 medicinal products containing recombinant DNA-derived proteins and derivatives to support a
75 Marketing Authorisation Application. Nevertheless, the principles explained in this document could
76 apply to other biological products, on a case by case basis.

77 This guideline does not address the comparability exercise for changes introduced in the manufacturing
78 process of a given product (i.e. changes during development and post-authorisation), as outlined by
79 ICH Q5E.

80 **3. Legal basis**

81 This guideline has to be read in conjunction with the introduction and general principles (4) and part II
82 of the Annex I to Directive 2001/83 as amended.

83 A full quality dossier (CTD Module 3) is required as detailed in current legislation and this should be
84 supplemented by the demonstration of biosimilar comparability, as discussed in this guideline.

85 Applicants should note that the comparability exercise for a biosimilar product versus the reference
86 medicinal product is an additional element to the normal requirements of the quality dossier and
87 should be discussed separately when presenting the data in Module 3.

88 **4. Manufacturing process of a similar biological medicinal** 89 **product**

90 The development and documentation for biosimilars should cover two distinct but complementary
91 aspects:

- 92 i) molecular characteristics and quality attributes (QA) of the target product profile should be
93 comparable to the reference medicinal product;
- 94 ii) performance and consistency of the manufacturing process of the biosimilar on its own.

95 The quality target product profile (QTPP) of a biosimilar should be based on data collected on the
96 chosen reference medicinal product, including publicly available information and data obtained from
97 extensive characterisation of the reference medicinal product. The QTPP should be detailed at an early
98 stage of development and forms the basis for the development of the biosimilar product and its
99 manufacturing process. It is important to identify critical quality attributes that may impact the safety
100 and efficacy of the product.

101 A biosimilar is manufactured and controlled according to its own development, taking into account
102 state-of-the-art information on manufacturing processes and consequences on product characteristics.
103 As for any biological medicinal product, the biosimilar medicinal product is defined by the molecular
104 composition of the active substance resulting from its process, which may introduce its own molecular
105 variants, isoforms or other product-related substances as well as process-related impurities. Potential
106 risks introduced by the proposed manufacturing process, as compared to the reference medicinal
107 product, should be kept in mind during the development of a biosimilar. For instance, the use of novel
108 expression systems should be carefully considered, as they may introduce additional risk, such as
109 atypical glycosylation pattern, higher variability or even a different impurity profile, as compared to the
110 reference medicinal product.

111 The formulation of the biosimilar does not need to be identical to that of the reference medicinal
112 product. The applicant should take into account state-of-the-art technology and, regardless of the
113 formulation selected, the suitability of the proposed formulation with regards to stability, compatibility
114 (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of
115 the active substance should be demonstrated. If a different formulation and/or container/closure
116 system to the reference medicinal product is selected (including any material that is in contact with the
117 medicinal product), its potential impact on the safety and efficacy should be appropriately justified.

118 The stability of the biosimilar product should be determined according to ICH Q5C. Any claims with
119 regard to stability and compatibility must be supported by data and cannot be extrapolated from the
120 reference medicinal product.

121 It is acknowledged that the biosimilar will have its own lifecycle. When changes to the manufacturing
122 process (active substance and/or finished product) are introduced during development, a comparability
123 assessment (as described in ICH Q5E) should be performed. For the purposes of clarity, any
124 comparability exercise(s) for process changes introduced during development should be clearly
125 identified in the dossier and addressed separately from the comparability exercise versus the reference
126 medicinal product. In addition, acknowledging the possible changes made to the process during the
127 development of the biosimilar product, it is advisable to generate the required quality, safety and
128 efficacy data for the biosimilar comparability study with product manufactured with the final
129 manufacturing process and therefore representing the quality profile of the batches to be
130 commercialised.

131 **5. Comparability exercise versus reference medicinal** 132 **product, quality aspects**

133 ***5.1. Reference medicinal product***

134 Several different batches of the reference medicinal product should be used to provide a robust
135 analysis and to generate a representative quality profile. The relative age of the different batches of
136 reference medicinal product should also be considered when establishing the target quality profile.

137 ***5.2. Comparability exercise***

138 An extensive comparability exercise will be required to demonstrate that the biosimilar has a highly
139 similar quality profile when compared to the reference medicinal product. This should include
140 comprehensive side-by-side analyses of the proposed biosimilar and reference medicinal product using
141 sensitive and orthogonal methods to determine not only similarities but also potential differences in
142 quality attributes. Any differences detected in the quality attributes will have to be appropriately
143 justified with regard to their potential impact on safety and efficacy. If significant quality differences at
144 the level of the active substance and/or the finished product are confirmed (e.g. atypical post-
145 translational structure for which an impact on safety or efficacy cannot be excluded), it may be very
146 challenging to claim similarity to the reference medicinal product, and thus, a full Marketing
147 Authorisation Application may be more appropriate. Alternatively, the applicant could consider
148 adequate revision of the manufacturing process to minimise these differences.

149 The aim of the comparability exercise is to demonstrate that the biosimilar product under development
150 and the reference medicinal product chosen by the applicant are similar at the level of the finished
151 product, i.e. the material that will be used to treat the patient. It is not expected that all quality
152 attributes will be identical and minor differences may be acceptable, if appropriately justified. Particular
153 attention should be given to quality attributes that might have a potential impact on safety or efficacy
154 (e.g. impact on immunogenicity or potency) or that have not been identified in the reference medicinal
155 product).

156 The applicant should demonstrate that the desired product and product-related substances present in
157 the finished product of the biosimilar are highly similar to that of the reference medicinal product.

158 Where quantitative differences are detected, such differences should be demonstrated to have no
159 relevance for the clinical performance of the product. Qualitative differences (i.e. presence or absence

160 of product-related substances and/or impurities) require a thorough justification, which may include
161 non-clinical and/or clinical data, as appropriate. It is however preferable to rely on purification
162 processes to remove impurities rather than to establish a preclinical testing program for their
163 qualification.

164 The target acceptance criteria used in the comparability exercise should be justified. Quantitative limits
165 should be established, where possible. The relevance of these limits should be discussed, taking into
166 account the number of reference medicinal product lots tested, the quality attribute investigated and
167 the test method used. These limits should not be wider than the range of variability of the
168 representative reference medicinal product batches, unless otherwise justified. A descriptive statistical
169 approach to establish target acceptance criteria for quality attributes could be used, if appropriately
170 justified.

171 It should be noted that acceptance criteria used for the comparability exercise versus the reference
172 medicinal product should be handled separately from release specifications (see also section 6 below).

173 As highlighted in section 4, it is advisable to generate the required quality, safety and efficacy data for
174 the biosimilar comparability exercise with product manufactured with the final manufacturing process.
175 While manufacturing changes may be expected during product development, it can be difficult to make
176 a robust comparison with the reference medicinal product and various batches of biosimilar material
177 manufactured using different/evolving processes.

178 It is acknowledged that the manufacturing process of the reference medicinal product may evolve
179 through its lifecycle, and may lead to detectable differences in some quality attributes. Such events
180 could occur during the development of a biosimilar medicinal product and may result in a development
181 according to a QTPP which is no longer fully representative of the reference medicinal product available
182 on the market. The ranges identified before and after the observed shift in quality profile could
183 normally be used to support the comparability exercise at the quality level, as either range is
184 representative of the reference medicinal product. Quality attribute values which are outside the
185 range(s) of variability measured in the different profiles of the reference medicinal product should be
186 appropriately justified with regard to their potential impact on safety and efficacy.

187 It should also be noted that there is no regulatory requirement for re-demonstration of biosimilarity
188 once the Marketing Authorisation is granted.

189 An overview of the comparability exercise performed at the quality level should be provided, and
190 should include an adequate description of the materials tested, the target acceptance criteria and
191 analytical methods used.

192 The materials used in the comparability exercise (i.e. biosimilar and reference medicinal product)
193 should be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the
194 reference medicinal product, number of batches, lot number, age of batches, use). Direct comparison
195 of the biosimilar to a publicly available standard, e.g. Ph. Eur., WHO, is not sufficient for the purpose of
196 comparability. Comparability should be demonstrated between the biosimilar and the reference
197 medicinal product with an established safety and efficacy profile.

198 **5.3. Analytical considerations**

199 Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference
200 medicinal products in parallel, to demonstrate with a high level of assurance that the quality of the
201 biosimilar is comparable to the reference medicinal product.

202 It is the responsibility of the applicant to demonstrate that the selected methods used in the
203 comparability exercise would be able to detect slight differences in all aspects pertinent to the
204 evaluation of quality. Methods used in the characterisation studies form an integral part of the quality
205 data package and should be appropriately qualified for the purpose of comparability. If applicable,
206 standards and reference materials (e.g. from Ph. Eur., WHO) should be used for method qualification
207 and standardization.

208 For some analytical techniques, a direct or side by side analysis of the biosimilar and reference
209 medicinal product may not be feasible or give limited information (e.g. due to the low concentration of
210 active substance and/or the presence of interfering excipients such as albumin). In such cases,
211 samples could be prepared from the finished product (e.g. extraction, concentration, and/or other
212 suitable techniques). Where such preparation techniques are used, the preparation should be outlined,
213 and the impact of the sample preparation process should be appropriately documented and discussed
214 (e.g. comparison of active substances before and after formulation/deformulation preparation).

215 **5.3.1. Physicochemical properties**

216 The physicochemical comparison comprises the evaluation of physicochemical parameters and the
217 structural identification of product-related substances and impurities. A physicochemical
218 characterisation programme should include a determination of the composition, physical properties,
219 primary and higher order structures of the biosimilar, using appropriate methodologies. The target
220 amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the
221 reference medicinal product. Any detected differences should be part of the micro-heterogeneous
222 pattern of the reference medicinal product. The N- and C-terminal amino acid sequences, free SH
223 groups and disulfide bridges should be compared, as appropriate. Any modifications/truncations should
224 be quantified and any intrinsic- or expression system-related variability should be described, set at the
225 minimum and justified.

226 If present, post-translational modified forms should be appropriately characterised. The carbohydrate
227 profile, comprising the overall glycan profile, site-specific glycosylation patterns as well as site
228 occupancy should be compared. The presence of unusual glycosylation structures (unusual
229 monosaccharides, linkages or sequences) or variants not observed in the reference medicinal product
230 may raise particular concerns and would require appropriate justification (see 5.2).

231 **5.3.2. Biological activity**

232 The comparability exercise should include an assessment of the biological properties of the biosimilar
233 and the reference medicinal product as an essential step in establishing a complete characterisation
234 profile. The biological activity is the specific ability or capacity of the product to achieve a defined
235 biological effect. Biological assays using different and complementary approaches to measure the
236 biological activity should be considered, as appropriate. Depending on the biological properties of the
237 product different assay formats can be used, e.g. ligand or receptor binding assays, enzymatic assays,
238 cell-based assays. Complementary approaches should be followed to accommodate the inherent
239 limitations regarding validation characteristics of single bioassays. For biological assays, it should be
240 demonstrated that the assay is sensitive and specific, and ideally sufficiently discriminatory to actually
241 detect changes in biological activity. The results of relevant biological assay(s) should be provided and
242 expressed in units of activity calibrated against an international or national reference standard, when
243 available and appropriate. These assays should comply with appropriate European Pharmacopoeia
244 requirements for biological assays, if applicable.

245 **5.3.3. Immunochemical properties**

246 In the case of monoclonal antibodies or related substances (e.g. fusion proteins based on IgG Fc), the
247 immunological properties should be fully compared. This should normally include comparison of
248 affinity of the products to the intended target. In addition binding affinity of the Fc to relevant
249 receptors (e.g. FcγR, C1q, FcRn) should be compared. Appropriate methodologies should be employed
250 to compare the ability to induce Fab- and Fc-associated effector functions.

251 **5.3.4. Purity and impurities**

252 The purity and impurity profiles of the active substance and medicinal product should be compared
253 both qualitatively and quantitatively by a combination of analytical procedures. Appropriate orthogonal
254 and state-of-the art methods should be used to compare the product-related substances and
255 impurities. This comparison should take into account specific degradation pathways (e.g. oxidation,
256 deamidation, aggregation) of the biosimilar product and potential post-translational modifications of
257 the proteins. The age/shelf life of the reference medicinal product at the time of testing should be
258 mentioned, and its potential effect on the quality profile should be discussed where appropriate.
259 Comparison of relevant quality attributes, tested at selected time points and storage conditions (e.g.
260 accelerated or stress conditions), could be used to further support the similarity of the degradation
261 pathways of the reference medicinal product and of the biosimilar.

262 Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, downstream impurities,
263 etc.) are expected to differ qualitatively from one process to another, and therefore, the qualitative
264 comparison of these parameters may not be relevant in the comparability exercise. Nevertheless,
265 state-of-the-art analytical technologies following existing guidelines and compendial requirements
266 should be applied, and the potential risks related to these newly identified impurities (e.g.
267 immunogenicity) will have to be appropriately documented and justified.

268 **5.3.5. Quantity**

269 Quantity should be determined using an appropriate assay, and should normally be expressed in the
270 same units as the reference medicinal product.

271 **6. Specifications**

272 As for any biotechnology-derived product, the selection of tests to be included in the specifications (or
273 control strategy) for both drug substance and drug product, is product specific and should be defined
274 as described in ICH Q6B: 'Note For Guidance on Specifications: Test Procedures and Acceptance
275 Criteria for Biotechnological/Biological Products'. The rationale used to establish the proposed range of
276 acceptance criteria should be described. Each acceptance criterion should be established and justified
277 based on data obtained from lots used in non-clinical and/or clinical studies, and by data from lots
278 used for the demonstration of manufacturing consistency, data from stability studies, any other
279 relevant development data and data obtained from the biosimilar comparability exercise (quality,
280 safety and efficacy).