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4 Guideline on similar biological medicinal products 5 containing recombinant granulocyte-colony stimulating 6 factor (rG-CSF)

7 Draft

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9
10 The proposed guideline will replace Annex to Guideline on similar medicinal products containing
11 biotechnology-derived proteins as active substance: Non-Clinical and Clinical Issues - Guidance on
12 Similar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor,
13 EMEA/CHMP/BMWP/31329/2005
14

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19 # Guideline on similar biological medicinal products
20 containing recombinant granulocyte-colony stimulating
21 factor (rG-CSF)

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39 # Executive summary

40 This guideline lays down the EU regulatory position on the non-clinical and clinical development of
41 recombinant granulocyte colony stimulation factor (rG-CSF) containing medicinal products claimed to
42 be biosimilar to an originator product approved in the Economic European Area (EEA). It is a revision
43 of the Guideline on Similar biological medicinal products containing recombinant granulocyte-colony
44 stimulating factor.

45 The non-clinical section provides guidance on *in vitro* pharmacodynamic studies and, if needed, *in vivo*
46 toxicological assessment. The clinical section provides guidance on pharmacokinetic and
47 pharmacodynamic studies and, if needed, a clinical immunogenicity study, as well as the risk
48 management plan. Whereas the previous version of this guideline requested a comparative clinical trial
49 in most cases, the revised guideline focusses on demonstration of biosimilarity based on a strong and
50 convincing physicochemical and functional data package and comparable pharmacokinetic and
51 pharmacodynamic profiles. In addition, the non-clinical section has been amended to follow a risk-
52 based approach. Specific considerations on pegylated rG-CSF have been included, where relevant.

53 # 1. Introduction

54 The marketing authorisation application dossier of a new recombinant Granulocyte Colony-stimulating
55 Factor (rG-CSF)-containing medicinal product claimed to be similar to a reference medicinal product
56 already authorised in the EU shall provide the demonstration of comparability of the product applied for
57 to this reference medicinal product.

58 Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one
59 threonine residue. Recombinant G-CSFs produced in E. coli (filgrastim) or in CHO-cells (lenograstim)
60 are in clinical use. Compared to the human and to the mammalian cell culture derived G-CSF, the E.
61 coli protein exhibits an additional amino-terminal methionine and no glycosylation. The rG-CSF protein
62 contains one free cysteinyl residue and two disulphide bonds.

63 Pegylated and non-pegylated versions of filgrastim-containing medicinal products are in clinical use.
64 Whereas pegfilgrastim can be administered subcutaneously only, non-pegylated filgrastim can also be
65 given intravenously. Compared to non-pegylated filgrastim, pegfilgrastim exhibits delayed and
66 prolonged absorption and elimination and consequently delayed onset and prolonged duration of
67 action.

68 Recombinant G-CSF is mainly eliminated by neutrophil-mediated clearance and, after saturation of this
69 pathway, by a low-rate, neutrophil-independent and linear pathway mediated by renal clearance.
70 Therefore, elimination of rG-CSF is more rapid with increasing neutrophil counts. Pegylation of rG-CSF
71 renders renal clearance insignificant, making the neutrophil-mediated clearance the predominant
72 elimination pathway.

73 The rG-CSF protein can be well characterised by state-of-the-art physico-chemical and biological
74 methods as can the polyethylene glycol (PEG) part of the molecule, where applicable. The development
75 of a biosimilar pegylated rG-CSF not only requires demonstration of similarity of rG-CSF but also of the
76 PEG part of the molecule including size, dispersity and binding site.

77 G-CSF stimulates the bone marrow to produce granulocytes and stem cells and their release into the
78 blood stream. It also stimulates the survival, proliferation, differentiation, and function of neutrophil
79 precursors and mature neutrophils. The clinical use of rG-CSF containing medicinal products is to
80 reduce the extent and duration of neutropenia (and consequently the risk of invasive bacterial and

mycotic infections) in patients with congenital, idiopathic, acquired or iatrogenic forms of severe neutropenia and the mobilisation of peripheral blood progenitor cells (PBPCs).

The effects of G-CSF on the target cells are mediated through its transmembrane receptor that forms homo-oligomeric complexes upon ligand binding. Several isoforms of the G-CSF receptor arising from alternative RNA splicing leading to differences in the intracytoplasmic sequences have been isolated. One soluble isoform is known. However, the extracellular, ligand-binding domains of the known isoforms are identical. Consequently, the effects of rG-CSF are mediated via a single affinity class of receptors.

Antibodies against rG-CSF appear to develop infrequently and have not been associated with relevant consequences for efficacy or safety. Antibodies against PEG, on the other hand, seem to be frequent, even in treatment-naïve patients, which may be explained by exposure to widely used PEG as well as PEG derivatives, e.g. in pharmaceutical and cosmetic products. Anti-PEG antibodies may potentially alter the pharmacokinetics and biodistribution of PEG-modified medicines. Safety issues related to anti-PEG antibodies have not been described.

2. Scope

The guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/2005 Rev. 1) addresses general aspects of establishing biosimilarity of such biological products in terms of safety and efficacy.

This product class-specific guideline presents the current view of the CHMP on the application of the main guideline for demonstration of biosimilarity of two rG-CSF-containing medicinal products.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the following requirements laid down in the EU Pharmaceutical legislation and relevant CHMP guidelines.

- Directive 2001/83/EC, as amended, in particular in Directive 2001/83/EC Art 10(4) and Part II of the Annex I of Directive 2001/83/EC, as amended
- Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMA/CHMP/BWP/247713/2012)
- ICH guideline S 6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (EMEA/CHMP/ 89249/2004)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)
- Guideline on Immunogenicity Assessment of Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006 Rev. 1)
- Guideline on good pharmacovigilance practices (EMA/500020/2012)

119 • Guideline on good pharmacovigilance practices, Module V – Risk management systems
120 (EMA/838713/2011)

121 4. Non-Clinical Studies

122 As regards non-clinical development, a stepwise approach should be applied to evaluate the similarity
123 of the biosimilar and reference medicinal product.

124 Non-clinical studies should be performed before initiating clinical trials. *In vitro* studies should be
125 conducted first and a decision then made as to the extent of what, if any, *in vivo* work will be required.
126 General guidance on the stepwise approach is provided in the "Guideline on similar biological medicinal
127 products containing biotechnology-derived proteins as active substance: non-clinical and clinical
128 issues". The approach taken will need to be fully justified in the non-clinical overview.

129 *4.1 In vitro studies*

130 In order to compare differences in biological activity between the similar and the reference medicinal
131 product, data from comparative bioassays should be provided, including receptor-binding studies and
132 functional assays (e.g. cell proliferation assay). Wherever possible, analytical methods should be
133 standardised and validated according to relevant guidelines.

134 *4.2 In vivo studies*

135 Generally, *in vivo* studies in animals are not recommended.

136 Measurement of pharmacokinetic and pharmacodynamic parameters is expected to be included in
137 clinical studies and similar studies in animals are usually not expected to contribute additional relevant
138 information to the biosimilarity exercise. Such studies as well as toxicological studies should only be
139 considered in specific cases, as explained in the "Guideline on similar biological medicinal products
140 containing biotechnology-derived proteins as active substance: non-clinical and clinical issues."

141 5. Clinical Studies

142 *5.1. Pharmacokinetic studies*

143 It is recommended to compare the pharmacokinetic (PK) properties of the test and the reference
144 medicinal product in healthy volunteers using subcutaneous administration. Additional clinical
145 pharmacology studies for intravenous use, if applicable, are not required.

146 In principle, cross-over or parallel-group PK studies are acceptable.

147 Typically, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tau}$ would be primary PK endpoints after single and multiple dose
148 administrations, respectively. Endogenous G-CSF plasma levels, although low, could lead to erroneous
149 exclusion of data. Therefore, in this context use of $AUC_{0\text{-}t}$ is preferable since the duration of plasma
150 sampling is based on the PD endpoint, which is considerably longer than needed for determination of
151 AUC for PK.

152 *Specifics for non-pegylated rG-CSF*

153 A multiple-dose study consisting of 5 consecutive daily administrations of test and reference,
154 respectively, is recommended. Due to the primary receptor-mediated clearance, which increases with

155 repeated administration, multiple-dose studies are considered more sensitive than single-dose studies
156 to detect potential differences in PK. In addition, PD response – especially with regard to CD34+ cell
157 count – is more robust with repeated administration. Daily doses of 5 mcg/kg/day are recommended to
158 detect potential differences in both PK and PD. The wash-out phase between periods in cross-over
159 studies should be sufficient (greater than 4 weeks) to avoid carry-over of pharmacological effects.

160 $AUC_{(0-t)}$ and C_{max} after last administration should be defined as primary PK endpoints. Secondary
161 endpoints should include $AUC_{(0-24)}$, C_{max} and T_{max} after first administration as well as AUC_{0-inf} and
162 terminal t½ after last administration.

163 A comparability range of 80-125% is considered acceptable without further justification.

164 ***Specifics for pegylated rG-CSF***

165 In principle, cross-over or parallel-group single-dose PK studies are acceptable. The intra-subject
166 variability of pegylated rG-CSF PK is considerably lower than the inter-subject variability. Hence, cross-
167 over studies decrease the notably high PK variability of pegylated rG-CSF but require a long wash-out
168 phase (at least 6 weeks) to avoid relevant carry-over of pharmacological effects. Studies with a parallel
169 group design on the other hand will require a higher number of study subjects to account for inter-
170 subject variability.

171 Measures to decrease PK variability are advisable. Female gender has been associated with –
172 apparently menstrual cycle dependent - increased PK variability which should be taken into account
173 when planning PK studies. Alternatively, it is acceptable to perform studies in male subjects only.
174 Injection site and injection technique should be standardised to decrease variability. Other factors that
175 may affect drug exposure are bodyweight and potentially anti-PEG antibodies. If pre-planned, a
176 subgroup analysis of subjects without pre-existing or treatment-emergent anti-PEG antibodies may be
177 acceptable for proof of similar PK profiles. However, a large difference in antibody development may
178 question biosimilarity.

179 A single dose in the range of 2 to 6 mg is considered suitable to detect potentially relevant differences
180 in both PK and PD. Care should be taken to administer similar protein amount of test and reference
181 products since the dose-exposure relationship is greatly overproportional and correction for protein
182 content using linear models is not appropriate.

183 $AUC_{(0-t)}$ and C_{max} should be defined as primary PK endpoints. Secondary endpoints should include
184 AUC_{0-inf} and terminal t½.

185 Due to the high PK variability and a rather flat exposure-response relationship, a comparability range
186 of up to 66-150% is considered acceptable but the point estimate will also be taken into account when
187 assessing PK similarity.

188 *5.2. Pharmacodynamic studies*

189 The pharmacodynamic (PD) effects of the test and the reference medicinal product should be assessed
190 as part of the PK study(ies). Pharmacodynamic endpoints are the same for pegylated and non-
191 pegylated products.

192 $AUEC_{0-t}$ and E_{max} of the absolute neutrophil count (ANC) should be the primary and $AUEC_{0-t}$ and E_{max} of
193 the CD34+ cell count the secondary PD endpoints. The PD parameters should be determined after the
194 last administration.

195 For all PD parameters, 95% confidence intervals should be calculated. The comparability limits for the
196 main PD parameters should be defined and justified prior to conducting the study; a comparability
197 range of 90-111% would be acceptable without further justification.

198 *5.3. Clinical efficacy studies*

199 Pivotal evidence for similar efficacy will be derived from the similarity demonstrated in
200 physicochemical, functional, pharmacokinetic and pharmacodynamic comparisons. A dedicated
201 comparative efficacy trial is therefore not considered necessary.

202 *5.4. Clinical Safety*

203 Provided the biosimilar and the reference product exhibit comparable physicochemical and functional
204 characteristics as well as comparable PK and PD profiles, those adverse events that are related to
205 exaggerated pharmacological effects (e.g. leukocytosis, splenomegaly, bone pain) can be expected to
206 occur at similar frequencies. Therefore, a dedicated safety study is not required.

207 Immunogenicity should be assessed as part of the pharmacology study(ies). Cross-over designs may
208 hamper the interpretability of the results. If analytical comparison, impurity profiles and/or antibody
209 results from the available study(ies) cast doubt on an acceptable immunogenic potential of the
210 biosimilar candidate, an additional parallel-group study with repeated administration and focus on
211 immunogenicity evaluation should be performed. The general principles, including guidance on how to
212 deal with pegylated proteins, is described in the Guideline on Immunogenicity assessment of
213 therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and should be followed.

214 6. Pharmacovigilance Plan

215 Within the authorisation procedure, the applicant should present a risk management plan in
216 accordance with current EU legislation and pharmacovigilance guidelines. The risk management plan of
217 the biosimilar should take into account identified and potential risks associated with the use of the
218 reference product. In addition, detailed discussion should be provided on how these safety concerns
219 will be addressed in post-marketing follow-up.

220 7. Extrapolation of indication

221 Considering that G-CSF has only a single mode of action, i.e. through binding to the G-CSF receptor,
222 demonstration of biosimilarity based on physicochemical and functional characterisation,
223 pharmacokinetic and pharmacodynamic profiles after subcutaneous administration and, where needed,
224 additional immunogenicity data will allow extrapolation to intravenous use and to other indications and
225 patient populations licensed for the reference product, if applicable.