EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte-colony stimulating factor

Agreed by Biosimilar Medicinal Products Working Party (BMWP)	June 2015
Adoption by CHMP for release for consultation	23 July 2015
Start of consultation	27 July 2015
End of consultation (deadline for comments)	31 October 2015

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

Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

Keywords	*Recombinant G-CSF, similar biological medicinal products, biosimilar, non-clinical studies, clinical studies*

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1. Introduction

The current Guidance on *similar medicinal products containing recombinant granulocyte-colony stimulating factor* provides recommendations for the non-clinical and clinical development of recombinant G-CSF claimed to be similar to a reference product already authorised in the EU. This guideline was one of the first product-class specific biosimilarity guidelines and came into effect in February 2006. Since then, several biosimilar filgrastims have been licensed in the EU. It is proposed to update the guideline based on the experience gained with marketing authorisation applications and scientific advices on biosimilar filgrastims.

2. Problem statement

Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one threonine residue. Recombinant G-CSF (rhG-CSF) produced in E. coli (filgrastim, not glycosylated) and CHO cells (lenograstim, glycosylated) are in clinical use. So far, only biosimilar filgrastim products have been applied for and licensed.

The current guideline includes recommendations for the development of biosimilar filgrastim and lenograstim. Pegylated rhG-CSF is not specifically addressed.

The current guideline requests at least one repeat dose toxicity study in a relevant species. However, a risk-based approach for *in vivo* animal studies has been implemented in the revised general 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) and other recently developed or revised biosimilarity guidelines.

The current guideline puts much emphasis on confirmatory clinical trials to compare efficacy and safety of the biosimilar and reference rHG-CSF. However, the revised “overarching” Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1) states the possibility that, in specific circumstances, a confirmatory clinical trial may not be necessary.

3. Discussion (on the problem statement)

The following aspects will need to be discussed and covered as appropriate by the revised guideline:

1. Considerations whether specific aspects with regard to the development of biosimilar pegylated rhG-CSF need to be included in the guideline.

2. The focus of the non-clinical comparability exercise is on in *vitro studies,* which are usually more specific and sensitive to detect differences between the biosimilar and the reference product than *in vivo* studies. For this reason and to avoid unnecessary animal studies, a risk-based approach is now generally accepted. It is suggested to adapt the guideline on biosimilar rhG-CSF containing products along these lines of thinking.

3. The revised “overarching” Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1) states prerequisites for waiving clinical trials. These conditions may be accomplishable for biosimilar rhG-CSF since structure, physicochemical characteristics and biological activity of G-CSF are well characterisable by state-of-the art methods and PD parameters of clinical relevance are available. Regulatory expectations to support a biosimilar rhG-CSF development without a confirmatory clinical trial will need to be further discussed and included in the guideline.

4. Recommendation

The Working Party recommends revising the *Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor* (EMEA/CHMP/BMWP/31329/2005). It is proposed to discuss an update of the non-clinical part of the guideline to include a risk-based approach for *in vivo* animal studies and for the clinical part to discuss the prerequisites for waiving a confirmatory clinical trial including clinical safety/immunogenicity. If considered appropriate, specific guidance for the development of pegylated filgrastim-containing biosimilars will be given.

5. Proposed timetable

It is anticipated that the draft revised guideline will be released for consultation in the first semester of 2016.

6. Resource requirements for preparation

The BMWP experts will develop the guideline. At least one formal meeting of the drafting group will be required in the margins of the working party meetings.

7. Impact assessment (anticipated)

Anticipated benefit for industry (revised and potentially reduced requirements) and assessors of biosimilar G-CSF-containing products.

8. Interested parties

- Pharmaceutical industry and competent authorities of the Member States.
- CHMP and its working parties, especially SAWP and Oncology WP.

9. References to literature, guidelines, etc.

- 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: quality issues (EMEA/CHMP/BWP/24771/2012)
- 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 immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)