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Pre-authorisation Evaluation of Medicines for Human Use

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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**GUIDANCE ON THE DESCRIPTION OF COMPOSITION OF
PEGYLATED (CONJUGATED) PROTEINS IN THE SPC**

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Guidance¹ on description of composition of pegylated (conjugated) proteins.

Background

The Biotechnology Working Party (BWP) of the Committee for Proprietary Medicinal Products (CPMP) has reviewed a number of pegylated recombinant proteins for marketing authorisation under the European Centralised Procedure. In its review, the BWP has identified that the basis for the statement of strength and composition in the SPC is not explicit.

In order to harmonise the approach to defining the qualitative and quantitative composition of this class of products, the Committee for Proprietary Medicinal Products and its Biotechnology Working Party and Efficacy Working Party has made the following position.

Also, in order to ensure clarity in these statements, the following terms are defined:

- Degree of modification: average number (a) of polymer molecules bound to the protein
- Mass definitions:
 - **Protein moiety (X)**: the molecular mass of protein contained in the protein conjugate
 - **Protein conjugate (Y)**: the average total molecular mass of the conjugated protein-polymer active substance
 - **Free protein**: the mass of the unconjugated protein

Position

a. To ensure a consistent composition of a protein conjugate, companies should utilise a range of physico-chemical analytical methods in the determination of the protein content as well as of the polymer content (such as polyethylene glycol polymer). The polymer reagent used in the manufacture should be well characterised, including determination of the polydispersity of mass. In the characterisation of the drug substance, the degree of modification and, where possible, the conjugation positions should be shown. Methods for routine verification of this higher order structure, including the corresponding total molecular size, should be selected and validated. Furthermore, methods should be in place for quantification of any free, unconjugated protein. Thus, the limits of the release specifications should be set to ensure consistency of the polymer conjugate, including polymer to protein molar ratio, although the assay used for routine determination of strength is usually based on the protein content.

b. Based on previous experience, where the determination of strength has been made on a protein content basis, the filling of the product is based on this parameter and that all dosing recommendations are based on the protein content, it is reasonable that the product literature reflects this while not neglecting the overall structure of the molecule. The Summary of Product Characteristics (SPC) of the protein conjugate should therefore include the mass of the protein moiety as well as a description of the protein conjugate.

However, the wording of the SPC where such information is mentioned should be carefully chosen, to avoid confusion between composition and activity of the protein conjugate as compared to the free protein.

¹ To be taken into account prospectively from the date of publication

Section 2 (Qualitative and quantitative composition) should mention:

- The composition expressed in accordance with the determination of strength, as assayed, with a clear indication that the amount relates to protein content only

and

- A description of the protein conjugate in the following way: The active substance is a covalent conjugate of < type of protein, production system > with <name of polymer contained in conjugate>.

The potency of this product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see 5.1

Section 5.1 (Pharmacodynamic properties) and **Section 5.2 (Pharmacokinetic properties)**

Section 5.1: The structure of the protein may be described as follows:

< type of protein> is conjugated with <name of polymer contained in conjugate> at a degree of substitution of <n moles of polymer/mole of protein>. The average molecular mass is approximately <Y> of which the protein moiety constitutes approximately <X>.

This may be followed by a description of isoforms when relevant, the molar activity of the conjugate compared with the non-substituted protein, differences in activity related to isoforms, etc.

Section 5.2: Comparative pharmacokinetic data with the non-conjugated protein may be shortly outlined when relevant, followed by a detailed description of the pharmacokinetics of the conjugate. When relevant, the behaviour of isoforms and stability of conjugates *in vivo* should be detailed.

The paper discusses pegylated proteins, which in their development have been declared and dosed based on their protein content, but the principles may be adopted to other protein conjugates with the same characteristics i.e. where the dosing and filling of a product is based in the protein content.