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Guideline on the declaration of the quantitative composition / labelling of biological medicinal products that contain modified proteins as active substance

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The concept paper for this guideline was published with the title "Concept paper on potency declaration/labelling for biological medicinal products which contain modified proteins as active substance" (EMA/CHMP/BWP/776563/2010).

Comments should be provided using this template. The completed comments form should be sent to GL-composition-modified-protein@ema.europa.eu

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Executive summary

This guideline outlines the approaches to be followed for declaring the quantitative composition / labelling of medicinal products that include modified proteins as their active substance, taking into account the product class and the clinically established declared value (e.g. international unit, mass unit) for the non-modified product, the method of assay (biological or physico-chemical), and relevance of the potency assay (i.e. correlated with clinical efficacy). For product labelling, it is considered important that the chosen unitage will not be confusing in clinical practice. The product information for healthcare professionals and patients must clearly differentiate the modified product from the non-modified product. This document also discusses the use of the activity unit to define a quality attribute during product manufacture and control.

1. Introduction (background)

There is an increasing interest of Industry to develop new biopharmaceuticals based on modifications of established protein therapeutics with the aim to modulate the in vivo properties of these products. The introduced structural modifications could be a removal or replacement of one, or a few, amino acids in the molecule, which is achieved by modification of the gene, or by chemical modifications such as conjugation to a carrier molecule applied after biosynthesis of the protein. Such products include pegylated forms of growth hormones, pegylated erythropoietins, and pegylated coagulation factors, as well as human serum albumin or Fc receptor portion as fusion protein for interferon alpha and coagulation factors. Pegylated products that have already been authorised include PegFilgrastim (ref1), PegInterferon-alpha (ref2), Methoxy polyethylene glycol-epoetin beta (ref3).

For complex biological medicines that cannot be fully characterised by physicochemical means, the established concept is to assign potency based on the use of an international standard for biological activity. The units of biological activity are mostly traced back to an internationally adopted reference preparation (International Standard, IS). The quantitative composition and dosing recommendation of biological medicinal products for which an IS exists is expressed in international units (IU).

Medicinal products containing modified proteins as their active substance are likely to be used in the same clinical context and indications as their parent compounds. However, since modified products are intentionally different from their parent compounds, they cannot always be standardized in a similar way against the International Standard developed for the parent compound. There is a risk that modified products could be considered as equivalent to the “parent” products in particular when they are intended for the same therapeutic indication and are given the same unitage as their parent counterpart. Therefore other approaches for potency assignments may be needed for modified products to assure proper usage of those products in clinical practice.

ICH Q6B (ref4) states: “The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilised. Where no such reference standard exists, a characterised in-house reference material should be established and assay results of production lots reported as in-house units.”

According to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards (ref 5), the behaviour of the reference standard should resemble as closely as possible the behaviour of the test samples in the assay used to test them. The general principle is that of “like versus like”.

These documents provide guidance about setting specifications for the potency of biological medicinal products and criteria for reference standards for the purpose of standardisation and control. Hence, the principles outlined in these documents only refer to standardisation and control but do not necessarily serve the purpose for declaring the content of the drug product and dosing recommendations. Different strategies as regards the unitage can be followed.

Modified products may have similar responses as their “parent” compounds in in vitro biological assays for potency assignment, where the structural modification(s) do not impact the relation between the tested molecule and its in vitro activity. Nevertheless, there may be a different correlation between units assigned in vitro and clinical response for the modified and the parent compound.

Companies define their own strategy for declaration of the quantitative composition / labelling and product information. Such strategies have to be scientifically valid and it is desirable to have a consistent approach within a product class. Therefore, thorough consideration should be given to the declaration of the quantitative composition / labelling of modified products.

EMA guidance documents related to aspects of potency labelling and declaration of composition for insulin analogues and pegylated proteins have been published (ref 6, 7). It should be noted that the current document does not replace these guidance documents but rather should be read in conjunction.

This document provides guidance about the various strategies that can be followed for the declaration of the quantitative composition / labelling of medicinal products that contain modified proteins as their active substance.

2. Scope

This guideline will apply to medicinal products that contain modified proteins as their active substance. In this respect, modified proteins refer to proteins that are intentionally modified (e.g. conjugated, pegylated or amino acid modifications), so that they are structurally different from their “parent” non-modified proteins and as a result behave differently in vivo.

However, the principles adopted and explained in this guideline may also be applicable to proteins not intentionally modified but having a different in vivo behaviour than their parent proteins or to modified proteins which have been modified for other reasons than changing their in vivo behaviour, (e.g. to improve production of the protein), and thus are expected to have the same in vivo behaviour as the parent protein.

3. Legal basis

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

4. Discussion

Strategies for declaration of the quantitative composition / labelling for biological medicinal products that contain modified proteins as active substance

Biological medicinal products are labelled in units of biological activity (IU or units) or mass units. Where mass units are used for the declaration of content, the specific activity (IU/mg or u/mg) is often specified as an additional quality attribute as part of the quality control strategy. The strategy to apply for modified proteins should therefore address two separate but evidently related issues:

A- the unit to declare (i.e. label) the content of a preparation

B- the activity unit to define a quality attribute during manufacture and control.

A: the unit to declare (i.e. label) the content of a preparation

The strategy for declaring the quantitative composition that would be acceptable for a product containing a modified protein will likely have to be considered on a case-by-case basis. Therapeutic proteins constitute a large number of products applied in a wide range of therapeutic areas and as such it may be difficult to follow a “one fits all approach”.

Three different situations are envisaged:

- Product labelling in mass units
- Product labelling in “in-house units”, i.e. the unitage is product specific
- Product labelling in International Units

<u>Product labelling in mass units</u>

Labelling in product specific mass units will be appropriate in situations:

- Where the quantitative composition of the parent compound is expressed on a protein content basis (e.g. in the case where physicochemical tests alone are used to quantitate the biological activity)
- Where the quantitative composition of the parent product is declared on the basis of units of biological activity but an equivalent declaration for the modified product is not desirable (for reasons given below). A declaration on a protein content basis is preferred, provided that the formulation and filling of the product is based on mass and all dosing recommendations (derived from clinical trials) are based on the protein content.

Where the active protein is conjugated to a carrier molecule the labelled mass should refer to the active protein part of the conjugate. The SmPC should explain the nature of the conjugate and also state the mass of the entire conjugate. Further guidance is given in the CPMP Guidance on the description of composition of pegylated (conjugated) proteins in the SPC (ref7).

Product labelling in product specific “in-house units”

Labelling in product specific “in-house units” will be appropriate in situations:

- Where the quantitative composition of the parent compound is expressed in units of biological activity and formulation and filling is based on units of biological activity and not on protein content.

and

- Where there is no International Standard for biological activity available or where the International Standard for biological activity is not appropriate for the modified product e.g. if statistically invalid estimates relative to the IS are obtained[1],
- Where a bio-assay, used to define the international standard, exists but the functional biological activity of the protein measured by this bioassay does not correlate to the clinical response.

In such cases, the establishment of a product specific activity unit is common and the assay results are reported as “in-house units” in accordance with ICH guideline Q6B (ref4). Accordingly, the product should then be labelled in “in-house units”.

Where an IS is available and shown suitable for the assay utilised for the modified product, the assay results could in principle be reported in International Units. However, in most cases the product is still labelled in product specific “in-house units” to prevent dosing errors.

Product labelling in International Units

Whilst in most cases product labelling will be in mass units or “in-house units”, there may be exceptional cases where for modified proteins it is desirable and justified to use product labelling in International Units. For coagulation factors used in replacement therapy, clinical efficacy is monitored in patients by measuring coagulation factor activity in post-infusion plasma samples in IU. For these products it has become common clinical practice to dose in IU. For these modified proteins the potency assay established for this product class should be used and the label claim should be in IU, depending on the validity of the assays relative to the IS (e.g. linearity, parallelism).

B: the activity unit to define a quality attribute during manufacture and control

For products where the content is declared in mass units as explained in section A above, there may still be a need to measure and assign biological activity as a quality attribute to appropriately control the quality/characteristics of the product, e.g. in the determination of specific activity.

As outlined in guideline ICH Q6B, for complex biological molecules, the physicochemical information may be extensive but unable to confirm all structural aspects relevant for biological activity such as the higher-order structure. In such cases, a biological assay should complete the testing of the drug substance and drug product wherever appropriate.

Nevertheless, where sufficient physicochemical information about the drug substance, including higher-order structure, can be thoroughly established by physicochemical methods, and relevant correlation to biological activity has been demonstrated, the application of a bioassay for the purpose of routine control at Drug Substance and/or Drug Product level, will not be needed.

In case of conjugated proteins consideration should be given to a situation where the use of a bioassay on the conjugate (Drug Substance, Drug Product) does not provide a valid potency calibration and thus

[1] For statistical evaluation reference is given to Ph.Eur. Chapter 5.3, Statistical analysis of results of biological assays and tests (ref 8)

an appropriate assay for the conjugate does not exist. In such cases physico-chemical characterisation of the conjugate should in any case complement the bioactivity specified for the protein before conjugation. As part of the quality control strategy, the substance before conjugation should be tested using the same assay as commonly applied for the parent protein and the unitage will be IU if an IS exists. Appropriate limits for bioactivity should be set.

4.1. Labelling / SmPC aspects

Quantitative composition of the modified product may be expressed in mass or “in-house units” or International Units as described above. The product information should explain that “in-house units” are product specific.

As for any medicinal product, the relationship between the quantitative composition of the modified product and clinically relevant parameters (e.g. pharmacokinetics and posology) will be established in clinical studies. Since the modified product is typically used in the same clinical indication as the non-modified product, it is important that the product information contains clear information for healthcare professionals and patients to differentiate the modified product from the non-modified product and avoid confusion in clinical use. The SmPC and package leaflet for the product containing the modified protein include an appropriate explanation of the relationship between the modified protein and the parent protein in terms of in vivo activity and pharmacokinetics and the consequences for posology. Useful information may also be found in the SSC/ISTH recommendations on the potency labelling of factor VIII and factor FIX concentrates (ref 9).

For example, Section 2 “Qualitative and quantitative composition”, Section 4.2 Posology and Methods of Administration, Section 5.1 Pharmacodynamic properties, and Section 5.2 Pharmacokinetic properties could contain further guidance in accordance to available regulatory documents SmPC guideline [ref10], Core SmPCs for human plasma and recombinant coagulation factors (ref11,12), QRD template, CHMP Guideline on potency labelling for Insulin analogue containing products with particular reference to the use of “International Units” or “Units [ref6], CPMP Guidance on the description of composition of pegylated (conjugated) proteins in the SPC [ref7]). For specific examples the European Public Assessment Reports (EPARS) of licensed products could be consulted.

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