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Biologics Working Party (BWP/CHMP)

Concept paper on potency declaration / labelling for biological medicinal products which contain modified proteins as active substance

Agreed by Biologics Working Party	December 2010
Adoption by CHMP for release for consultation	17 February 2011
End of consultation (deadline for comments)	17 May 2011

The proposed guideline will replace guideline / NfG Reference.[1]

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

Keywords	*Modified proteins, potency, International Standard* [2]

[1] If this supersedes a previous guideline – otherwise delete.
[2] To be identified here during preparation of the concept paper - keywords represent an internet search tool - Rapporteurs to propose and Working Party/Committee to adopt.

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1. Introduction

There is an increasing interest of Industry to develop new biopharmaceuticals based on modifications of established protein therapeutics with the aim to alter the *in vivo* properties of these products. The introduced 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 (e.g. pegylation) applied after biosynthesis of the protein. Some of these modified products have already entered the market, many more are in clinical development.

Well known examples of modified products are insulin analogues and pegylated (PEG) proteins. EMA guidance documents related to aspects of potency labelling and declaration of composition for these classes of compounds have been published (ref 1, 2).

Currently, more representatives for PEG modified biopharmaceuticals are under development, e.g. pegylated coagulation factors. The issue of calibration / standardisation and labelling of such products has been the subject of a number of Scientific Advices given by CHMP.

Modified products could be considered as analoguous to the “parent” products in particular when they are intended for the same therapeutic indication and are given the same activity unitage as their parent counterpart, leading to potential confusion and misinterpretation in the dosing in daily practice. Thorough consideration should be given to the expression of strength of modified products in units of activity. Modified products will likely have similar responses as their “parent” compounds in *in vitro* biological assays for potency assignment, where the structural modification(s) do not modify the interaction between the test molecule and the effector. Nevertheless, units thus assigned *in vitro* may correlate differently with the clinical activity for the modified and the parent compound, particularly if the modification has changed the pharmacokinetic profile.

This concept paper aims to provide the rationale for drafting a guidance document for potency assignment of modified proteins for which an International Standard exists or where a clinical recognised unit exists (without an International Standard established) for the non-modified product.

It should be noted that the terminology “modified proteins”, used throughout this concept paper, refers to proteins which are modified in any way (e.g. pegylated or amino acid modifications) in order to alter the *in vivo* properties of these molecules. The terminology “parent product” refers to the non-modified protein which the modified protein is derived from and for which the first (International) Unitage has been established.

2. Problem statement

The strength of established biological medicinal products as well as their dosing recommendation is often expressed in units of biological activity. These units are mostly traced back to an internationally adopted reference preparation. The strength and dosing recommendation of biological medicinal products for which an international standard exists is expressed in international units (IU).

Medicinal products containing modified proteins as their active substance will likely be applied in the same clinical context and indications as their parent compounds. However, since modified products are intentionally different (both in terms of molecular profile and bioactivity) from their parent compounds, they cannot be standardized in a similar way against the International Standard established and used for the parent compound. Therefore other approaches for strength assignments should be developed for modified products. At present companies define their own strategy for strength and specific activity declaration. This situation challenges the approved concept of an international standard for biological activity and the lack of a harmonised approach could raise confusion in clinical dosing. On the other

hand the usage of conventional “International Units” for the labelling of modified product is not an option since it bears the risk to mislead physicians and patients when there is no strict equivalence, in terms of bioactivity or half-life, for example, despite a possible equivalence in the *in vitro* potency assay.

Also, it is necessary to harmonise the policy of content assignment and labelling with the Ph.Eur. The latter is already the case for several insulin analogues. At this moment there are no monographs for other types of modified proteins.

3. Discussion (on the problem statement)

Several biopharmaceuticals are now being developed with the aim to alter the *in vivo* properties of these products. Such products include pegylated forms of growth hormones, pegylated erythropoietins, and pegylated coagulation factors, as well as human serum albumin as fusion protein for interferon alpha and coagulation factors. PEGylated products that have already been authorised include PegFilgrastin, PegInterferon-alpha, Methoxy polyethylene glycol-epoetin beta.

The Guidance on the Description of composition of pegylated (conjugated) proteins in the SPC[2] discusses pegylated proteins that in their development have been declared and dosed based on the protein content. According to this guidance, the composition should be expressed in accordance with the determination of strength, as assayed, with a clear indication that the amount relates to protein content only. The Summary of Product Characteristics should also state that the potency of the product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. The focus of the guidance is molecular mass rather than units of activity in a biological assay.

According to ICH guideline Q6B, “The results of biological assay should be expressed in units of activity calibrated against an international or national reference standard. Where no such reference standard exists, a characterised in-house reference material should be established and assay results reported as in-house units.”

In strict interpretation, labelling with International Units (IU) should exclusively be used for those substances for which an International Standard (IS) has been established. As a consequence, unless an IS is established for a specific modified protein, it should be labelled in units rather than international units of the parent substance.

Following discussion on the validity of the use of International Units for insulin analogues, it was decided to introduce substance-specific units for assignment and labelling of insulin analogues. Whilst for most insulin-analogue the International Unit for human insulin has been used for their initial potency assignment of the analogue reference standard, the actual labelling and potency expression is based on in-house units without reference to the IS.

Based on the information provided by industry, a similar approach had been followed for some pegylated proteins. Companies did use an International Standard from the parent substance to establish the potency of the pegylated product/substance. However, an activity unit for the pegylated product might not be directly comparable in clinical use to the IU for the non-pegylated products. This is because the pegylated product is a different chemical substance compared to the non-pegylated product and is designed to have different pharmacokinetic and eventually pharmacodynamic properties. At the same time, using an International Standard for the parent compound to calibrate a reference standard for the modified protein still might give a good indication on "where to start" the dosing of the modified product. Indeed, the approach taken for the insulin analogues could be very well suited for the other modified proteins.

Whilst the issue on potency declaration would also be applicable to new "directly" modified products (i.e. where the non-modified compound has not been developed) or chimeric proteins, where the strength may be expressed in units of biological activity or mass depending on the assay method, these products are not within the scope of the guidance document.

Ideally, for each new compound with strength expressed in units of biological activity, theoretically, a new IS could be developed but this would obviously take great efforts in the case of conjugated proteins since different modifications can be build in for one parental protein leading to many ISs. A WHO and/or compendial standard for conjugated material would only be beneficial if it could cover several sources. This will have to be assessed on a case-by-case basis.

As described above, a common approach is to define the bioactivity on the basis of mass units of the protein moiety of the modified product, as in the case of some pegylated proteins. Though in most cases a bioassay would still be needed to "quantify" the bioactivity of the modified protein (related to the non modified counter part), the switch towards mass unit may be made at the time of starting non-clinical studies (e.g. pharmacodynamics, pharmacokinetics) to support clinical trial and dose finding in humans. As outlined in ICH Q6B, a biological assay to measure the biological activity of the product may be replaced by physicochemical tests under certain conditions. Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

Whether or not units of biological activity or mass will be accepted in clinical dosing practice might depend on the clinical experience/habits with use of the IU and specific types of products, i.e. when physicians are used to prescribing in IU they may not readily wish to “convert” to mass units. Similarly, where products are self-administered for chronic conditions, patients may be reluctant to change.

Currently, there is no overall guideline available which provides a harmonised approach for declaring potency / labelling of modified proteins.

4. Recommendation

It is recommended that the CHMP/BWP reviews the current guidelines “on potency labelling for Insulin analogue containing products with particular reference to the use of “International Units” or “Units”(EMEA/CHMP/BWP/124446/2005) and “on the description of composition of pegylated (conjugated) proteins in the SPC, EMEA/CPMP/BWP/3068/03” with respect to the issue described above. Subsequently, an updated / new guideline should be developed that describes the approaches to be followed for declaring potency / labelling of modified proteins taking into account the nature of the protein (i.e. complexity), the modification applied, as well as the established role of the declared value (e.g. international 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).

The principles adopted and explained in the guideline will apply to all biological medicinal products which include modified proteins as their active substance for which an International Standard exists or where a clinical recognised unit exists (without an International Standard established) for the non-modified product.

5. Proposed timetable

It is aimed that a guideline for consultation can be adopted by the end of 2011 by BWP/CHMP, followed by a 6-month consultation period.

6. Resource requirements for preparation

A BWP/BPWP/CHMP drafting group has been formed, which can meet on the margins of the BWP meetings. In addition, discussions can be taken forward progressively through other means (email correspondence, Vitero meetings if necessary). One rapporteur will be appointed.

7. Impact assessment (anticipated)

The document will provide essential guidance to harmonise the policy on expression of potency declaration of medicinal products containing modified proteins as their active substance. The document will take into account the current situation of potency labelling for products already on the market but will particularly be aimed at products under development. Consistency of approach towards declaration of potency is considered beneficial as regards to clinical dosing.

8. Interested parties

WHO, European Pharmacopoeia, Haemophilia patient organisations and Haemophilia treater organisations will be consulted during the development of the guideline. As some of the modified products under clinical development concern modified coagulation factors, it is also recommended to consult the BPWP.

9. References to literature, guidelines, etc.

1. CHMP Guideline on potency labelling for Insulin analogue containing products with particular reference to the use of “International Units” or “Units, EMEA/CHMP/BWP/124446/2005

2. CPMP Guidance on the description of composition of pegylated (conjugated) proteins in the SPC, EMEA/CPMP/BWP/3068/03