EMA/CHMP/BWP/692937/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the declaration of the quantitative composition / potency labelling of biological medicinal products that contain modified proteins as active substance' (EMA/CHMP/BWP/85290/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

	Name of organisation or individual
1	SciencePharma Chelmska 30/34 00-725 Warsaw, Poland
2	Group of Experts 6B, European Pharmacopoeia Department, European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
3	EBE (European Biopharmaceutical Enterprises)

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	None	
2	The European Pharmacopoeia (Ph. Eur.) Group of experts 6B appreciates that their comments and proposals on the concept paper with respect to coagulation factors were considered by the drafting group and are reflected accordingly in the draft guideline. It is important to note that it is recommended that for labelling purposes the International Unit should be used if valid assays, versus the International Standard, are obtained.	Partially agreed. As explained in the GL, the use of IU for labelling is considered suitable for only specific medicinal products, i.e. clotting factors in replacement therapy, containing modified proteins as their active substance. A case-by-case evaluation approach is needed.
3	EBE welcomes the opportunity to comment this guideline. We will like to emphasise the importance of allowing a case-by-case evaluation, always taking into account what is reasonable and the central point should always be to ensure safety for the patient. It is important to recognise that the use of in house units on labels can be extremely confusing for healthcare providers when manufacturers of similar products create completely different in house units - since a unit suggests some form of comparability from one product to another and thus should actually be discouraged. We recommend that abbreviations are explained and that a consistent wording regarding potency and biological activity is used (At present there is a switch	Agreed. Partially agreed. In fact, the same kind of confusion could occur with the used of IU. Indeed, it is important that the labelling should not be confusing for healthcare providers. Therefore, the product information should provide adequate details and explain that “in-house units” are product specific. It is noted that the use of product specific units has become common practice for insulin analogues. The comment is acknowledged and document will be revised to explain abbreviations and using consistent wording regarding potency and biological activity, where appropriate.

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	from potency used in section 1 to biological activity as used in section 4).	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 37-41	3	**Comment:** The introduction describes in the scope of modified proteins either products with alternate amino acid sequences or conjugated proteins. Another category should include glycoengineered proteins, which can have clinically significant differences in potency and bioavailability. **Proposed change (if any):** "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, by chemical modifications such as conjugation to a carrier molecule applied after biosynthesis of the protein, or by engineering of existing post-translational modifications for enhanced functionality or bioavailability".	Agreed. Intended modification based on glycoengineering would fit into the guideline scope. Clear examples for post-translational modification not presented. However, glycol engineering will be included as an example.
41	1	Comment: A clarification is proposed. It is suggested to mention that products listed in the lines 42-44 are only examples of envisaged protein modifications.	Partially agreed. The products mentioned refer to the structural modifications mentioned in lines 39-41. As indicated under "Scope" other modifications could be introduced. Text will be revised.
Lines 81 - 84 and lines 156 - 163	3	Comment: It is stated that this new guideline should be read in conjunction with the already existing guidelines (reference 6 and 7). In these guidelines it is stated that the potency of modified proteins cannot be declared in IU based on the native	Partially agreed. The comment about the reference to existing guidelines is noted but the current guideline is not considered contradictive as it mentions the exceptional case for coagulation factors for replacement

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		protein. This is inconsistent with the text in lines 156-163 in this new guideline, where it is possible to express the potency in IU. However we support the text in lines 156-163 opening the possibility for using IU for coagulation factors in replacement therapy. Proposed change (if any): We recommend that the wording “modified proteins” in line 158 is replaced by “coagulation factors used in replacement therapy” as it is not common use for the modified insulins. Furthermore, the existing guideline from CPMP on description of PEGylated proteins SPC (EMEA/CPMP/BWP/3068/03) should be revised to include the possibility for labelling the potency expressed in IU of PEGylated and non-PEGylated protein of the same therapeutic class when this is feasible within the assay method applied.	therapy. Agreed. Not agreed. As explained, the use of IU could be applied in the exceptional case of coagulation factors for replacement therapy only.
82	1	Comment: It is proposed to include the provisions of the 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, ref. 6) as it specifically refers to the same aspect as the drafted guideline.	Comment not fully comprehended. Stakeholder has not presented a specific proposal for change. Nevertheless, the provisions of the “insulin analogue” GL are based on the provisions of the ICH guideline Q6B mentioned in the section “Product labelling in product specific “in-house units”, which are mentioned in the current guideline.
Line 89-92	3	**Comment:** Same comment as for lines 37-41.	Agreed.

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		Proposed change (if any): "In this respect, modified proteins refer to proteins that are intentionally modified (e.g. conjugated, pegylated, post-translationally modified or amino acid modifications), so that they are structurally different from their "parent" non-modified proteins and as a result behave differently in vivo."	
94	1	Comment: A clarification is proposed. It is suggested to explain what kind of 'proteins not intentionally modified' are meant. It would be helpful to explain what protein modifications are considered as not-intentional.	Agreed that section is not fully clear and will be updated.
Line 105-108	3	**Comment:** As noted in general comments, potency is often expressed as relative activity when an international potency standard is not available. **Proposed change (if any):** " Where mass units are used for the declaration of content, the specific activity (IU/mg or u/mg) or the relative potency (% relative to an in-house standard) is often specified as an additional quality attribute as part of the quality control strategy."	Agreed.
122-163	1	Comment: It is proposed to clarify that product labelling in mass unit should be taken into consideration as a priority. This can be deduced from the guideline but it is not expressed clearly enough. In this context it is not entirely clear why the way of expressing the quantitative composition of the parent compound is given as the first factor to be taken into account	Not fully agreed. The strategy for declaring the quantitative composition should be based on a case-by-case as outlined in the document. No strict priority is given for each of the strategies described, although it is, for example, mentioned that "...A declaration on a protein content basis is preferred, provided that the

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		when setting labelling of the modified product.	formulation and filling of the product is based on mass and all dosing recommendations (derived from clinical trials) are based on the protein content.”.
Lines 124 – 126	3	Comment: Many products are labelled in mass units even though a biological assay is used as part of the control strategy to confirm that these mass units have the expected biological activity. The current text does not seem to consider this possibility. Proposed change: Modify the text in parentheses as follows: (e.g. in the case where physicochemical tests alone are used to quantitate the biological activity, **or when a biological assay is used as part of the control strategy to confirm that the declared mass units show the expected biological activity**)	Partially agreed. The possibility of labelling in mass units while the biological activity is measured as part of the control strategy is described in Section B of the document. Not agreed, the control strategy should not (necessarily) be linked to the labelling strategy.
129	1	Comment: A clarification is proposed. It is not clear which ‘reasons given below’ should be taken into consideration.	Agreed.
Lines 140 - 142	3	Comment: It is a well-known fact, that the analytical variation for determination of bioactivity by e.g. clot or chromogenic assays for coagulation factors is much greater than the analytical variation for determination of mass by e.g. HPLC. This implies that mass determination of a given drug substance batch will give a better estimate of the true batch content than biological assay (as usually reflected by stricter acceptance criteria for content as compared to biological activity). The following	Partially agreed. The comments about assay variability are appreciated but will have to be considered on a case-by-case basis. The sentences 140-141 are not intended to indicate that formulation and filling should be done on the basis of biological activity units instead of mass units, but to refer to the situation where the quantitative composition of the parent compound is expressed in units of biological

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		conditions are normally considered for determining filling based on mass or potency: • If the variation of the specific bioactivity corresponds to the analytical variation filling based on mass is highly recommended. If the filling instead was performed based on potency a much larger batch to batch variation is expected. • If the variation of the specific bioactivity is significantly wider than the analytical variation filling based on bioactivity should be considered. Even though the product may be labelled in units, content (and potency) consistency could be better assured by filling based on mass if the product specific bioactivity corresponds to the variation of analytical methods. As this guide only covers labelling and not manufacture it is consequently proposed to delete the last part of the bullet in lines 140-142 and revise to: Proposed change: • Where the quantitative composition of the parent compound is expressed in units of biological activity.	activity and formulation and filling is based on units of biological activity and not on protein content. However, the current sentence is apparently subjected to misinterpretation and will be revised.
147	1	Proposed change: Where a bio-assay, used ~~to define the international standard~~ <u>for the non-modified product</u>, exists but the functional biological activity of the <u>modified</u> protein measured by this bioassay does not correlate to the clinical response.	Partially agreed. Situation applies both to modified and parent protein.
147-149	3	**Comment**: If there is no link between the bio-assay used to define the	Partially agreed. Ideally, a correlation between the results from the in vitro bioassay and

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		international standard and the clinical response, it is debatable whether that international standard is suitable for its purpose. This can only be acceptable, if a completely new clinical indication is developed for an existing compound for which an international standard has been established. This explanation needs to be added to clarify this requirement. **Proposed change (if any):** Add: This will be the case if a completely new clinical indication is developed for an existing compound for which an international standard has been established.	clinical response is obtained. However, there may be a situation where the bioassay is not directly relevant or related to the mode of action (e.g. IFN bioassay).
Lines 161-163 "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 assay relative to the International Standard (linearity, parallelism)."	2	Comment: The sentence refers to a potency assay which is specific for a product class, e.g. the assay(s) described in the Ph. Eur. However, products could be developed which could not be measured with this product class specific assay. In this case other assays for labelling must be applied. For this purpose Group 6B likes to refer to the recommendation of the SSC for FVIII and FIX (Hubbard et al. 2013). Proposed change (if any): "*For these modified proteins the potency assay established for each product in this class should be based on thorough characterisation of the modified product with respect to potency assays. The label claim should be in IU, provided the validity of the assay relative to the International Standard*	Partially agreed. Proposed change will be slightly reworded to also address additional issues to the use of IU.

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		(linearity, parallelism) is established."	
Line 172-175	3	**Comment:** The exemption for application of a potency assay in cases of a well-characterized biologic applies only to the measurement of quantity (total activity) of drug product. This exemption does not apply to the requirement in ICH Q6B that a potency assay should be used as a measure of quality. Current text reads: "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." But ICH Q6B reads (at §4.2.4) "A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological and biological drug substance and/or drug product. When an appropriate potency assay is used for the drug substance, ***an alternative method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product.*** However, the rationale for such a choice should be provided." (emphasis added) **Proposed change (if any):**	Partially agreed. However, current wording does reflect the European approach towards DS and DP routine control of some well-characterised products (e.g. somatropins, insulins)

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		"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 of quantitative assessment of Drug Product will not be needed."	
Line 192	3	**Comment:** Guidance recommends including 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 in the Patient Leaflet as well as the Summary Product Characteristics (SmPC). To permit consistency in the "lay language" used with regard the description of the modified protein we ask the agency to provide several examples. This will encourage consistency and minimize rework of patient leaflet text on this topic. **Proposed change (if any):** We recommend providing examples for the industry to use when developing lay language description.	Not agreed. Although the comment is appreciated, the current document is not intended to provide more detailed guidance on labelling and reference is made to other published EMA documents.
Lines 197-204	3	Comment: The section is a list of other documents and the readability is low. Proposed change (if any): Please, present the information as a list.	Agreed.