European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON POTENCY LABELLING FOR INSULIN ANALOGUE CONTAINING PRODUCTS *WITH PARTICULAR REFERENCE TO THE USE OF "INTERNATIONAL UNITS" OR "UNITS"*

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	European Federation of Pharmaceutical Industries and Associations - EFPIA	EU

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
None		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
None		
EXAMPLE:		
1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
First § Second sentence	The sentence should be completed as appropriate. Suggestion is made to change the sentence: "*These changes could be a removal or replacement of one, or a few, amino acids in the molecule, which are achieved by modification of the gene, or other chemical modifications*." To read: "*These changes could be a removal, <u>an addition</u>, or replacement of one, or a few, amino acids in the molecule, which are achieved by modification of the gene, or other chemical modifications*."	It has been accepted to include <u>*an addition*</u> to the text
First § Third sentence	The sentence should be more precise. Suggestion is made to change the sentence: "*The purpose of the molecular change is to alter the in vivo properties of human insulin to obtain for instance a faster or a slower action of the insulin*." To read: "*The purpose of the molecular change is to alter <u>the absorption rate</u> of*	The proposed replacement of ~~*in vivo* properties~~ with <u>*the absorption rate*</u> has not been endorsed. Although, it is for the time being fully correct that the analogues are developed with intention to have a different absorption rate compared to human insulin, other parameters could be altered in the future. The wording <u>*the absorption rate*</u> is therefore considered to be too narrow. It is proposed to keep *in vivo* properties with the addition *e.g. the absorption rate*.

	human insulin to obtain for instance a faster or a slower action of the insulin."	
2 Recommendation		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Second and third §	After the first § (on salient issues), the document should clearly differentiate the quality and the labelling aspects: Quality: From "Labelling with International Units…" To "...reported as in-house units" The following paragraphs will cover the Labelling aspect.	The proposal has been accepted and the headings "Quality aspects" and "Labelling / SmPC aspects" are introduced in the document.
Second §	Clarification needed in paragraph: Labelling with International Units (IU) should exclusively be used for those insulins for which an International Standard has been established, e.g. human insulin. In consequence, unless an International Standard is established for an insulin analogue, it should be labelled in units. Proposed rewording of last sentence to: "In consequence, unless an International Standard is established for an insulin analogue, potency should be labelled and reported as in-house units."	The proposal has been accepted. The term "in-house unit" gives a more unambiguous and clear message.

Fourth §	Labelling: The in-house units established for insulin analogues are drug substance specific units. One analogue unit may not be equivalent to one IU of human insulin or one unit of a different insulin analogue. To help physicians and patients, we recommend to: - enclose in the SmPC a correspondence (relationship) between the in-house units and the International Units of human insulin (section 2) - improve special warnings of SmPC (section 4.4.) - enclose in vivo comparison data between the product specific units and known standards in section 5.1. Pharmacodynamics. Suggestion is made to replace the sentence "*As the in-house unit established for insulin analogues are drug substance specific units…insulin analogues*". by "*The in-house units established for insulin analogues are drug substance specific units. One analogue unit may not be equivalent to one IU of human insulin or one unit of a different insulin analogue*." Suggestion is made to replace the sentences: "*It is therefore recommended that the SPC and package leaflet for insulin analogues should include an appropriate explanation of this issue as it applies to the particular product concerned, for example:* *- "The potency of this preparation is stated in units. These units are exclusive to <product name> and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics)*". by "*It is recommended that the SmPC and package leaflet for insulin analogues include:*	The proposed replacements are not accepted besides the proposed wording *"one analogue unit may not be equivalent to one IU of human insulin or one unit of a different insulin analogue."* which was incorporated in the text. Otherwise the text remained unchanged. The main purpose of this guideline is to give the message that: • Human insulin has a potency, which is established based on an International Standard and therefore human insulin is labelled in IU. • Insulin analogues are developed with the intention to have an altered effect (e.g. fast or slow adsorption, different pharmacokinetic) compared to human insulin and the use of IU is therefore not appropriate. • Glucose lowering effect is the only parameter, which, could be compared between insulin human and insulin analogues and among different insulin analogues. However, measuring of glucose lowering effect would not reflect the difference in total pharmacological action.

	- *a correspondence between the in-house units and the International Units of human insulin (section 2. Qualitative and Quantitative composition) based on an in vivo biological assay such as intravenous infusion.* - *special warnings for changing from one preparation to another (section 4.4 Special warnings and special precautions for use), for example:* *"Switching a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may require a change in dosage.* *Although the correspondence referred to above between in-house units and International Units may establish the relative glucose-lowering efficacy of insulin analogues at the molecular level, the clinical effect of each preparation depends also on its formulation. See section 5.1. (Pharmacodynamics)"*	The proposed warning statement is too detailed and might give the impression that changes of product should be avoided. The following warning statement for incorporation in the SmPC section 4.4 "Special warnings and special precautions for use" has been adopted: *"Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose."* The proposal was not accepted. It refers only to formulation differences between different analogues (soluble vs. isophane or crystalline) and not to pharmacological differences resulting from molecular changes (see introduction).