European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

DISCUSSION IN THE BWP	October 2003 December 2003 February 2004 March 2004 May 2004 June 2004 September 2004
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INTRODUCTION

Insulin analogues are a group of insulin where the molecule of human insulin has been changed. 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. The purpose of the molecular changes is to alter the *in vivo* properties of human insulin to obtain for instance a faster or slower action of the insulin.

Recent Marketing Authorisation applications have featured differences between the units employed by manufacturers for expressing the potencies of medicinal products containing insulin analogues, including the manner in which the potency units are expressed in the product information for these products. This observation raises the following questions:

- What are the correct units for expressing the potencies of these preparations? or
- Is IU an appropriate unitage for expressing insulin analogue potency?

Recommendation

There are two salient issues:

- The International Standard for human insulin has been developed solely for use in the determination of the potency of human insulin products and it's development did not encompass its use for the purpose of determining the potencies of insulin analogues.
- Insulin analogues may differ significantly from underivatised human insulin with respect to their pharmacokinetic and pharmacodynamic properties.

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 labeled in units.

This recommendation is in line with 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."

As the in-house unit established for insulin analogues are drug substance specific units, analogue units are not comparable between different insulin analogues. 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)"