EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin

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| Agreed by Biosimilar Medicinal Products Working Party (BMWP) | June 2011 |
| Adoption by CHMP for release for consultation | 21 July 2011 |
| End of consultation (deadline for comments) | 30 September 2011 |

The proposed guideline will replace Annex to Guideline on similar medicinal products containing biotechnology-derived proteins as active substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Human Insulin, EMEA/CHMP/BMWP/32775/2005.

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

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| Keywords | Recombinant human insulin, insulin analogues, similar biological medicinal products, non-clinical studies, clinical studies |

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# 1. Introduction

The current Guidance on Similar Medicinal Products containing Recombinant Human Insulin provides recommendations for the development of recombinant soluble (short-acting) human insulin claimed to be similar to a reference product already authorised in the EU. This guideline came into effect in June 2006 but, so far, no biosimilar insulin has been licensed in the EU. Three products applied for by the same Applicant were withdrawn prior to Opinion.

# 2. Problem statement

More recently, several EMA scientific advices on the development of biosimilar insulins, particularly insulin analogues, have been requested. Insulin analogues and long-acting human insulin preparations are currently not covered by the above guideline. In addition, different study populations, study designs and insulin doses have been proposed for the pivotal PD study (clamp study). Moreover, the guideline does not appear to be clear on whether the PK study can be combined with the PD study. Questions were raised regarding the most suitable patient population and size of the clinical safety study. It has also been questioned whether non-clinical studies would always be needed in the development of biosimilar insulins.

# 3. Discussion (on the problem statement)

Although similar considerations and scientific principles may apply to biosimilar insulin analogues and long-acting human insulin preparations as to soluble insulins, some thoughts may need to be given to the sensitivity of the clamp study for detection of potential differences in the duration of action or other summary measures between long-acting insulin formulations due to the flat PK profile of these insulins and high variability in the tail part of the clamp study. In addition, further considerations regarding the study population (patients with type 1 diabetes versus healthy volunteers), study design (e.g. with versus without basal insulin infusion) and insulin dose in the clamp study could be included. It may be clarified that the comparative PK evaluation is usually expected to be part of the clamp (PD) study. It could also be clarified that no formal non-inferiority testing for antibody frequency is expected in the safety study and that inclusion of patients with type 1 and type 2 diabetes may be appropriate. Regarding non-clinical requirements, a risk-based approach may be introduced.

# 4. Recommendation

The Working Party recommends revising the *Guidance on Similar Medicinal Products containing Recombinant Human Insulin* (EMEA/CHMP/BMWP/32775/2005) to include insulin analogues and long-acting human insulin preparations in the guideline. As part of this revision, the Working Party will also discuss the inclusion of considerations on the new risk-based approach for non-clinical data requirements as well as further clarifications and considerations regarding clinical studies as mentioned in section 3 above.

# 5. Proposed timetable

It is anticipated that the draft revised guideline will be released for consultation in the first semester of 2012.

## 6. Resource requirements for preparation

The BMWP experts will develop the guideline. At least one formal meeting of the drafting group will be required in the margins of the working party meetings.

## 7. Impact assessment (anticipated)

Anticipated benefit for industry (clear and more detailed requirements) and assessors of biosimilar insulin-containing products.

## 8. Interested parties

- Pharmaceutical industry and competent authorities of the Member States.
- CHMP and its working parties, especially SAWP.

## 9. References to literature, guidelines, etc.

- Part II of the Annex I of Directive 2001/83/EC, as amended
- Guideline on similar biological medicinal products (CHMP/437/04)
- Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- ICH topic S6 - Note for guidance on Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)