Reviewer's report

Title: Bioequivalence of two recombinant erythropoietin formulations in patients with anemia due to end-stage renal disease on hemodialysis: A parallel, randomized, double blind study

Version: 1 Date: 22 December 2004

Reviewer: Huub Schellekens

Reviewer's report:

General
This study shows the relative high level of biotechnology research and development in Cuba. Also the efforts of our colleagues to develop affordable biotech drugs for the developing world should be supported.
The setup, performance and analysis of the study meet the necessary scientific standards.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The authors apply the bioequivalence approach of a classical drug to a protein. However this is invalid. The consensus is that preclinical and clinical data are necessary for the registration of these follow-up protein products. According to the EMEA guidelines (re)issued in december 2003 concerning bioequivalence of biotech proteins and the clinical annex, biosimilarity has to be shown for quality, safety and efficacy. Concerning the efficacy the comparison should be done for every indication in phase III studies. The conclusion that can be drawn from this study is therefore very limited. The results are insufficient to conclude that the Cuban epo is equivalent to the Eprex and can be safely used as an alternative. The authors should clearly state this in their paper and reformulate why the study was done and what the conclusions are.

2. The choice of comparator is remarkable. This formulation of Eprex is longer on the market since 1998. Either this study is done before 1998 or the Eprex used was out-of-date. The authors should clarify this choice.

3. There is no mention at all of immunogenicity, although according to EMEA guidelines this should always be discussed. This is the more remarkable because the concern regarding immunogenicity is based on the experience with Eprex. The formulation change in 1998 led to about 225 cases of antibody mediated pure red cell aplasia. A risk analysis and strategy of evaluation and assay methodology would be an essential part of development of any new epo and therefore should be included in this paper.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

There are a number of minor remarks, mainly typo's or misspellings. But as I recommend major
revision, these may disappear or become irrelevant.

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No

**Declaration of competing interests:**

I have participated in meetings and publication sponsored by Amgen, Roche and J&J which produce epo’s. I have no other financial or other competing interests.