At its 18th meeting, held on 3 June 2002 at the European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy, the ECVAM Scientific Advisory Committee (ESAC) unanimously endorsed the following statement:

Taking into account the Comment (Annex 1) of the ECVAM Task Force on the Quality Control of Hormones and Related Products, which had been submitted to the European Pharmacopoeia Secretariat on 16 April 2002, and also taking into account Article 7(3) of Directive 86/609/EEC, which clearly states that in a choice between experiments, those which use the minimum number of animals … cause the least pain, suffering, distress, and lasting harm and which are most likely to provide satisfactory results shall be selected, the Committee notes that the test in normocythaemic mice (Method B; according to the revision proposal of European Pharmacopoeia Monograph 1316) provides all the information that is required, while causing less suffering and distress than the test in polycythaemic mice (Method A). The Committee considers that the relevant authorities should take this into account during the ongoing revision of the Monograph.

Michael Balls
Head of Unit
ECVAM
Institute for Health & Consumer Protection
Joint Research Centre
Ispra, Italy

Eva Hellsten
Head of Unit C.3
DG Environment
European Commission
Brussels, Belgium

28 June 2002
1. The ESAC was established by the European Commission, and is composed of representatives of the EU Member States, industry, academia and animal welfare, together with representatives of the relevant Commission services. The following members of the ESAC were present at the meeting on 3 June 2002:

Dr Bas Blaauboer (ERGATT)  Mr Michael Balls (ECVAM - Chairman)
Dr Philip Botham (ECETOC)  Mr Jürgen Vogelgesang (DG ENV)
Dr Argelia Castaño (Spain)  Mr Juan Riego Sintes (ECB)
Dr Bernward Garthoff (EFPIA)  Mr Enrico Sabbioni (ECVAM)
Professor André Guillouzo (France)  Mr Andrew Worth (ECVAM - Secretary)
Dr Maggy Jennings (EUROGROUP for Animal Welfare)
Professor Elisabeth Knudsen (DK)
Dr Roman Kolar (EUROGROUP for Animal Welfare)
Dr Odile de Silva (COLIPA)
Professor Horst Spielmann (Germany)
Dr Annalaura Stammati (Italy)
Professor Eric Tschirhart (Luxembourg)
Dr Matti Viluksela (Finland)
Professor Erik Walum (Sweden)

2. Members of the ECVAM Task Force on the Quality Control of Hormones and Related Products: Bernward Garthoff (Bayer, D), Marlies Halder (ECVAM, I), Coenraad Hendriksen (RIVM, NL), John Mulders (Organon, NL) and Jacob van Noordwijk (Chairman, NL).


Background information to the two methods allowed by the European Pharmacopoeia (Ph. Eur.) for the batch potency testing of *Erythropoietin Concentrated Solution* (Revision proposal of Monograph 1316):

The revision proposal on *Ph. Eur.* monograph 1316 has been published in *Pharmeupopa*, the European Pharmacopoeia Forum, in January 2002. It includes two methods for the batch potency testing of erythropoietin concentrated solution (Annex 2, pp. 98-99), which can equally be used:

**Method A** is carried out in polycythaemic mice and “the activity of the preparation is estimated by examining, under given conditions, its effect in stimulating the incorporation of $^{59}$Fe into circulating red blood cells of mice made polycythaemic by exposure to reduced atmospheric pressure”.

**Method B** is carried out in normocythaemic mice and “the assay is based on the measurement of stimulation of reticulocyte production in normocythaemic mice”.

Method A is of special animal welfare concern since it involves a 14-day treatment of the mice in a hypobaric chamber, which induces suffering and distress. In addition, the total experimental period of Method A is with 21 days much longer than for Method B with four days.
Dear Madam/Sir

Please find attached a comment on the monograph:

Erythropoietin concentrated solution (PA/PH/Exp. 6/T(01) 17 ANP)

This comment represents the opinion of the ECVAM Task Force on the Quality Control of Hormones. Members of the TF are: Bernward Garthoff (Bayer, D), Marlies Halder (ECVAM, I), Coenraad Hendriksen (RIVM, NL), John Mulders (Organon, NL) and Jacob van Noordwijk (Chairman, NL).

Best regards

Marlies Halder (signed)

cc Michael Balls (Unit Head, ECVAM)
Kees van Leeuwen (Director, IHCP)
Annex 1 continued

Comments on PA/PH/Exp. 6/T (01) 17 ANP

Pharmeuropa 14, 94-99

Assay

The current draft allows the use of Method A or Method B. Method A is considered to involve more distress on the mice than Method B, since the mice are treated in a hypobaric chamber.

The European Convention ETS 123 and Directive 86/609/EEC clearly state that … in a choice between experiments, those which use the minimum number of animals … cause the least pain, suffering, distress, and lasting harm and which are most likely to provide satisfactory results shall be selected…

In the light of this, only Method B should be used and we therefore recommend to delete Method A from the monograph.