17 March 2011
EMA/CHMP/SWP/169839/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the Need for Revision of the Position on the Replacement of Animal Studies by *in vitro* Models (CPMP/SWP/728/95)

Agreed by Safety Working Party	February 2011
Adoption by CHMP for release for consultation	17 March 2011
End of consultation (deadline for comments)	30 June 2011

The proposed Guideline will replace the Position on Replacement of Animal Studies by *in vitro* Methods (CPMP/SWP/728/95).

Comments should be provided using this template. The completed comments form should be sent to swp-h@ema.europa.eu

Keywords	*reduction, replacement, refinement, in vivo, in vitro, validation, regulatory acceptance*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

A Position on the Replacement of Animal Studies by *in vitro* Models was adopted by the Committee for Medicinal Product for Human Use (CHMP) in February 1997 [1]. This paper addresses the feasibility of replacing *in vivo* animal studies by *in vitro* investigations in the non-clinical development of medicinal products. Furthermore, considerations regarding validation procedures for *in vitro* methods and their incorporation into CHMP guidelines are presented.

Over the past years a shift has been observed towards the regulatory acceptance of scientifically valid *in vitro* methods as well as formally validated *in vitro* methods as part of an integrated testing strategy. Moreover focus has broadened to the application of all 3 R's, replacement, reduction and refinement, whilst historically much emphasis has been placed only on replacement of animal studies by one or more *in vitro* or in silico approaches. Large EU initiatives such as the European Centre for the Validation of Alternative Methods (ECVAM) and the European Partnership for Alternative Approaches to Animal Testing (EPAA) facilitate progress in this field. Finally, the application of all 3 R's is currently embedded the drafting process of non-clinical regulatory guidance both at EMA and ICH level.

2. Problem statement

In vitro methods are already an integral part of the non-clinical testing programme of human medicinal products, either as pivotal, supportive or as exploratory studies. Moreover, approaches aiming at reducing or refining animal studies are routinely implemented in regulatory guidelines, where applicable. As such, although regulatory acceptance of 3R alternatives is currently possible via multiple and flexible approaches, at present there is no clearly defined process for regulatory acceptance of all 3R alternatives (refinement, reduction and replacement).

Taking into account the progress in the field of the 3R's as described above, a thorough revision of the Position on the Replacement of Animal Studies by *in vitro* Models [1] is needed in order to ensure that:

the focus is extended to include replacement, reduction and refinement alternatives.

a process for regulatory acceptance of all 3R alternatives (replacement, reduction and refinement) is described.

different possible approaches for regulatory acceptance of 3R alternatives are clearly described, and therefore the need for formal validation studies *versus* proof of scientific validity should be discussed.

if applicable, formal validation requirements are updated according to the current state-of-the-art.

the legal requirements related to the application of the 3Rs as per Directive 2010/63/EC are adequately reflected.

This revision includes a change in title of the guideline to be developed as compared to the current position paper in order to take into account the above considerations.

3. Discussion (on the problem statement)

The field of the 3 Rs has significantly evolved since the Position on the Replacement of Animal Studies by *in vitro* models was adopted in 1997 [1].

Although non-clinical studies still heavily rely on animal data, adherence to the 3Rs principles is clearly evident both at the EU and ICH level.

Various *in vitro* test systems are currently used for different purposes and at different time-points within the non-clinical development programme. These include both formally validated tests (e.g. 3T3 NRU phototoxicity test [2], *in vitro* micronucleus test [3]) and *in vitro* methods that have been 'historically' introduced or models for which there is sufficient scientific validity based on accumulated experiences (e.g. *in vitro* genotoxicity tests [3], hERG assay [4]). Additionally, supportive mechanistic data are predominantly obtained in *in vitro* models of proven scientific validity (e.g. mitochondrial toxicity of HIV drugs) [5]. And finally, the use of *in vitro* methods for the purpose of compound screening by pharmaceutical companies is subject only to in-house validation.

In addition, the introduction of tailor-made non-clinical testing strategies, involving both *in vivo* and *in vitro* testing, in the recently adopted ICH guidelines M3 (R2) [6] and S9 [7] is expected to entail a significant reduction of animal use. At the EU level, the recognition that data obtained in traditional single dose toxicity studies are of limited value and that information on acute toxicity can be obtained in other types of toxicity studies, led to the removal of the 3BS1a Single Dose Toxicity guideline [8]. This will reduce the number of animals used for testing and will contribute to animal welfare.

Finally the introduction of *in silico* approaches (e.g. DEREK [9]) as part of a tiered non-clinical testing strategy also contributes to a reduction of animal use.

The full revision of Directive 86/609/EC was recently completed and resulted in the adoption of Directive 2010/63/EU on the protection of animals used for scientific purposes on 3 June 2010 [10]. This Directive will take effect on 1 January 2013. Different articles relate to the application of the 3R's. As such, article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure[1].

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

Also article 13 states that:

1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

2. In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:

(a) use the minimum number of animals;

(b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;

(c) cause the least pain, suffering, distress or lasting harm;

and are most likely to provide satisfactory results.

[1] A 'procedure' means any use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with the good veterinary practice [10].

Therefore, the Position on the Replacement of Animal Studies by *in vitro* Models [1] should be thoroughly revised (including a change in title) in order to take into account scientific and legislative progress and to formulate guidance on when and how 3R alternatives (replacement, reduction and refinement) can be considered for regulatory acceptance.

4. Recommendation

The CHMP recommends revising the Position on the Replacement of Animal Studies by *in vitro* Models [1] (including a change in title) in order to propose a clear process for regulatory acceptance of 3R alternatives (replacement, reduction and refinement) in regulatory non-clinical testing of medicinal products in line with current scientific progress and legislative requirements.

5. Proposed timetable

It is anticipated that a draft of the revised guideline may be released for consultation in 2011.

6. Resource requirements for preparation

The preparation of this guideline will involve the Safety Working Party of the CHMP and if appropriate an *ad hoc* working group on this area.

7. Impact assessment (anticipated)

The revised guideline is expected to provide clear information on the conditions and strategy for regulatory acceptance of 3R (replacement, reduction and refinement) alternative methods. This is anticipated to facilitate regulatory acceptance of 3R alternatives and thus to reduce animal use in non-clinical testing conducted to support the conduct of clinical trials and marketing authorisation.

8. Interested parties

Animal welfare organisations and relevant research organisations on alternative approaches to animal testing.

9. References to literature, guidelines, etc.

1. Position adopted by the CPMP on 19 February 1997 on Replacement of Animal Studies by *in vitro* Methods (CPMP/SWP/728/95).
2. Note for Guidance on Photosafety Testing (CPMP/SWP/398/01).
3. Note for Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human Use (EMEA/CHMP/ICH/126642/2008).

4. Note for Guidance on the Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (CPMP/ICH/423/02).

5. Reflection Paper on *in vitro* Investigation of Mitochondrial Toxicity of Anti-HIV Nucleoside Reverse Transcriptase Inhibitors (EMEA/CHMP/SWP/8212/2007).

6. Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95).

7. Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008).

8. Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity' (EMA/CHMP/SWP/81714/2010).

9. Questions and answers on the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/SWP/431994/2007 Rev. 3)

10. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276/33).