Recommendations of the ECVAM Workshop on „Alternatives to Animal Testing in the Quality Control of Immunobiologicals; State of the Art and Future Prospects“

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Abstract

With regard to the principles of Replacement, Reduction and Refinement, art. 23[1] of the Council Directive 86/609/EEC on the Protection of Animals used for Experimental and other Scientific Purposes, is of utmost importance. This article states that „The Commission and Member States .... should take steps ... to encourage research into the development and validation of alternative techniques ...“.

In order to carry into effect this article, the Commission of the European Communities (EC) has established the European Centre for the Validation of Alternative Methods (ECVAM) on October 29, 1991. The centre is located at the Joint Research Centre (DG XI) at Ispra (Italy), its first director is Michael Balls from the UK.

The main goal of ECVAM is to promote the regulatory acceptance of alternative methods which are of importance to the biosciences and which reduce, refine or replace the use of laboratory animals. The activities of the centre are focussed on facilitating, co-ordinating, supporting and/or organizing international validation studies, preferably in collaboration with other bodies.

A working programme has been made for 1993 and 1994 by ECVAM's scientific advisory committee. Animal testing in the quality control of vaccines was selected as one of the area's of interest. As a first step it was decided to organize a workshop, with the aim to evaluate potential alternatives, to identify obstacles in development, validation and implementation and to discuss possible solutions.

The workshop was held in Utrecht, April 16-17 and the 20 invited participants came from national control laboratories, regulatory bodies, vaccine manufacturers and academic world.

The main conclusions and recommendations in the field of the quality control of *veterinary* vaccines are summarized below:

- Whenever possible, tests for potency, based on lethality or clinical symptoms should be replaced by other test models such as models based on serology or *in vitro* test sytems.
- When experimental challenge is unavoidable, clear clinical symptoms should be regarded equal to lethal end-points and animals should be humanely euthanised.
- It was recommended to look at possibilities to shift the use of the standard method for potency testing to stages of the production before the final bulk and to perform simplified *in vivo* tests on final bulks or final lots (e.g. purified bulk Tetanus toxoid) or to characterize the final bulk or final lot by *in vitro* methods.
- The validation studies performed with regard to replacement of the NIH test in rabies vaccine potency testing by *in vitro* test systems were considered to be insufficient and rather conflicting. Further investigation will be required. It was recommended to evaluate a single dilution protection test, supplemented by *in vitro* tests as a possiblealternative for the existing titration method and the use of end-points others than death.
- With regard to the Clostridial vaccines (apart from tetanus) it was concluded that, although serological models have been described as a replacement to the protection tests, no interlaboratory validation studies have been performed yet. Before these studies are organized, a number of questions should be clearified, such as the design of a validation study, the preparation of reference sera, relation between protective antibody levels in the target species and potency in IU/ml etc. The European Pharmacopoeia (EP) was asked to organize a workshop or task-force to identify obstacles and to draft a validation strategy.
- To eliminate the test on abnormal toxicity when doing the safety test. In case this test can not be omitted,

1 The Commission and Member States should encourage research into the development and validation of alternative techniques which could provide the same level of information as that obtained in experiments using animals but which involve fewer animals or which entail less painful procedures, and shall take such other steps as they consider appropriate to encourage research in this field.

the test should be performed on the final bulk instead of on the final lot.

* The safety test as such was considered to be a useful test, but combination with the potency test in the target species; either by a double-dose potency test or a single-dose safety test, was strongly recommended.
* To omit the mouse safety test in the EP monograph on inactivated swine Erysipelas vaccine.

It was felt by the participants of the workshop that criteria for validation procedure are urgently needed. A flow-chart for validation was presented. It was recommended that interlaboratory validation procedures should be discussed with, and organized by the EP.

The workshop ended to conclude that, although the number of research activities towards replacement of tests involving the use of animals increases, it is believed we can not do without animal tests in the near future, in particular for vaccine quality control purposes. It was emphasized by the participants of the workshop that the humane use and care of laboratory animals in vaccine quality control should be guaranteed. A set of guidelines, adopted by regulatory bodies such as EP and WHO, could be helpful in this respect. They express the concern of the scientific community on the welfare of experimental animals and sets guidelines for humane treatment and implementation of the 3R concept.

The guidelines are commended initially as a model to international regulatory agencies and national control authorities and for them to adapt as appropriate.

Guidelines for the humane use and care of animals were drafted and will be submitted to the EP secretariat and the WHO as a discussion paper.

The content of this abstract reflects the opinion of the participants of the workshop, and not necessarily the official view of the European Centre for the Validation of Alternatives Methods (ECVAM). It should also be noted that the abstract is not officially approved by the participants of the workshop.

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Liebe Leserinnen und Leser,

das Erscheinen des ersten ALTEX-Supplementband ist für uns Anlaß, über die inhaltliche Struktur von ALTEX nachzudenken. In den Heften 1 bis 3/94 erschienen 10 Hauptartikel, für das Heft 4/94 sind 5 Artikel vorgesehen. Zwölf zusätzliche Artikel, wie sie das Supplement 1 enthält, müßten wir praktisch über ein Jahr verteilen. Dies hätte eine große Einbuße an Aktualität zur Folge. Wir werden also nicht umhin können, zu bestimmten Schwerpunktthemen Supplementbände herauszubringen. Bei der ohnehin sehr knapp kalkulierten Preisgestaltung von ALTEX werden wir dazu aber immer einen Sponsor brauchen. Diesmal hat sich dankenswerterweise der Bundesverband für Tiergesundheit e.V. bereit erklärt, einen Teil der Kosten zu tragen. Der Verband muß die neuesten Entwicklungen und Möglichkeiten bei der versuchstier- oder besser gesagt bei der belastungsfreien Entwicklung von Impfstoffen im Auge behalten und seinen Mitgliedern zugänglich machen. Auch das Bundesministerium für Forschung und Technologie ist am behandelten Thema interessiert. Es hat viele der in diesem Heft vorgestellten Projekte und den Workshop am PEI gefördert. Dem Spektrum Akademischer Verlag sei an dieser Stelle ebenfalls gedankt. Ohne das großzügige Entgegenkommen des Verlages wäre es nicht möglich gewesen, dieses Supplement kostenfrei an die Abonnenten von ALTEX abzugeben.

Alle Artikel wurden begutachtet und redaktionell überarbeitet. Es werden bei der Impfstoffprüfung sehr belastende Tierversuche erwähnt. Zum Teil sind es ältere Versuchsreihen, zum Teil aber auch Versuche, die auf den noch immer gültigen internationalen Prüfvorschriften beruhen und die zum Vergleich und zur Betonung der Notwendigkeit einer Weiterentwicklung zitiert werden müssen.

Es befriedigt uns in der Redaktion zutiefst, daß wir auf dem Gebiet der Impfstoffentwicklung so gute Fortschritte dokumentieren dürfen. Wir wünschen uns noch viele ähnliche Erfolgsmeldungen.

Wo Licht ist, gibt es natürlich auch Schatten. Wir sollten die Problematik der Entwicklung und Prüfung von Veterinärimpfstoffen nicht diskutieren, ohne einen weiteren Tierschutzaspekt dabei wenigstens zur Diskussion zu stellen. Da bei Tieren in der Landwirtschaft, die ja üblicherweise zur Gewinnung von Lebensmitteln gehalten werden, der Antibiotikaeinsatz sehr limitiert ist, sind es natürlich die Impfstoffe, die eine intensive Tierhaltung weiterhin möglich machen. Alternativen zur Entwicklung und Prüfung von Veterinärimpfstoffen zu fördern, sollte nicht gleichgesetzt werden mit einer Zustimmung zu allen Formen der Nutztierhaltung.

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