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## **ECVAM      European Centre for the Validation of Alternative Methods**

### **STATEMENT ON THE RELEVANCE OF THE TARGET ANIMAL SAFETY TEST FOR BATCH SAFETY TESTING OF VACCINES FOR VETERINARY USE**

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)<sup>1</sup> unanimously endorsed the following statement:

Following a review of a scientific report<sup>2</sup> and a publication<sup>3</sup> on the relevance of the target animal safety test (TAST) for the batch safety testing of veterinary vaccines, it is concluded that the requirement for the TAST should be waived for routine batch release.

The Committee welcomes the fact that the revision proposal for the European Pharmacopoeia General Monograph, *Vaccines for Veterinary Use*, now states that "*for an established vaccine the routine application of the safety test may be waived by the competent authority in the interests of animal welfare when a sufficient number of consecutive batches have been produced and found to comply with the test, thus demonstrating consistency of the manufacturing process. Significant changes to the manufacturing process may require resumption of routine testing to re-establish consistency*".<sup>4</sup>

In the light of this, the Committee recommends that a retrospective and scientific analysis of available TAST data for each vaccine should be undertaken, in the expectation that, if no batch had been found to fail in the TAST for a sufficient number of recent batches, the TAST could be waived for future batches.

The ESAC has been regularly kept informed of the progress of the review, and this endorsement was based on an assessment of various documents, including, in particular, the final report on the TAST study by the Advisory Group on Alternatives to Animal Testing in Immunobiologicals (AGAATI),<sup>2</sup> which has been submitted for publication in *Biologicals*.<sup>3</sup>

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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. ECVAM (2001). Final report of the study contract No 134 10-97-11 F 1EI ISP NL: *Evaluation of the relevance of the safety test for the quality control of veterinary immunological medicinal products*. 122 pp.
3. Cussler K. & Halder M. (2002). The target animal safety test - Is it still relevant? *Accepted for publication in Biologicals*
4. Council of Europe (2001). Vaccines for Veterinary Use. *Pharmeuropa* **13**, 363-369.

## **General information about the study on the evaluation of the relevance of the target animal safety test (TAST):**

### *A. Rationale for the study*

During the last few years, the relevance of the target animal safety test (TAST) has increasingly been questioned (1-10). The introduction of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) into the production of vaccines has significantly increased their safety and quality. Thus, some of the animal tests carried out for purity and safety purposes appeared to be superfluous. ECVAM took up this issue and in 1997 commissioned the Advisory Group on Alternatives to Animal Testing in Immunobiologicals (AGAATI) to perform the study, *Evaluation of the relevance of the target animal safety test for the quality control of veterinary immunological medicinal products (contract 134 10-97-11F 1 EI ISP NL)*.

### *B. Objectives*

The main objectives of the study were: a) to identify the monographs, directives and guidelines in the European regulatory framework, which stipulate the TAST; b) to analyse and critically review the purpose of the TAST; c) to perform a retrospective analysis of TAST data; and d) to give recommendations, based on the outcome of the retrospective analysis, for modifying the relevant monographs and guidelines.

### *C. Results*

The TAST is stipulated by 52 European Pharmacopoeia (*Ph. Eur.*) monographs on veterinary immunologicals, by three European Union (EU) *Directives* and various EU guidelines, to be carried out on the finished product. At least two animals of the target species are injected with twice (inactivated vaccines) or ten times (live vaccines) the recommended dose of the vaccine to be tested. None of the animals should show abnormal or systemic reactions during a given observation period. There are significant differences between the individual *Ph. Eur.* monographs in terms of the numbers of animals required (mammals: 2 animals; poultry and fish: at least 10 animals), the administration scheme and the period of observation, and also between the numbers of animals stipulated in the *Ph. Eur.* monographs on fish vaccines (10 fish) and the EU guidelines (30 fish).

Based on an inquiry, data were collected from seven (out of 23) OMCLs and 14 manufacturers. During the period 1994-1997, 11,185 vaccine batches were submitted for batch release and the OMCLs tested 670 of these batches in the TAST (665 passed, 4 passed after retesting, 1 failed). In total, 82 of these batches were not released; however, in only one case was this due to failure in the TAST. The data received from the 14 manufacturers covered the years from 1997-1999. 11,386 batches were tested in the TAST, all of which passed, except that 215 passed only after retesting and 7 failed.

### *D. Conclusions and Recommendations*

- The results of this study show that the TAST as a routine batch test is no longer relevant for the safety of immunobiologicals. Vaccine batches are hardly ever rejected because of failure in the TAST. Therefore, the TAST should be omitted as a routine batch control test.
- In special cases, where the TAST might still be required (for example, for new products or for a certain period after licensing, or for vaccines which caused serious pharmacovigilance problems), clear guidance should be given on the test design (animal number, dosage) and on the evaluation criteria (acceptable/non-acceptable local and systemic reactions, test repetitions).

- The general *Ph. Eur.* monograph, *Vaccines for Veterinary Use*, should be revised and the TAST should be deleted as a routine batch control test. In cases where the TAST is considered still to be needed, guidance should be given on the test design and evaluation criteria.
- The Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Evaluation Agency (London, UK) should revise the EU guidelines for immunobiologicals, and should delete the TAST as a routine batch control test.
- The TAST should immediately be deleted from those *Ph. Eur.* monographs for which sufficient evidence is available to justify its deletion (for example, for clostridial vaccines, erysipelas vaccines, immunosera).
- The Group of Experts 15V of the European Pharmacopoeia Commission and the Immunological Veterinary Medicinal Working Party (IWP) of the CVMP should work on the harmonisation of the TAST requirements in the *Ph. Eur.* and in the EU guidelines, and should provide harmonised general guidance on the test design and evaluation criteria for those products or cases where the TAST would still be considered necessary.
- The Pharmacovigilance Working Party of the CVMP should provide an annual pharmacovigilance report for all immunobiologicals in the EU, and should discuss the results with the IWP, to ensure that existing and arising safety concerns for specific products and/or product groups could be adequately addressed.
- The Safety Testing Working Party of the Veterinary International Cooperation on Harmonisation should include harmonisation of batch safety testing of immunobiologicals in its work programme.

#### E. Follow-up

The general *Ph. Eur.* monograph, *Vaccines for Veterinary Use*, is currently being revised, and the proposal for revision has been published in *Pharmeuropa* (11). The revision proposal suggests the requirement for the TAST to be waived after consistency of production has been demonstrated. In July 2001, ECVAM submitted comments on this proposal to the *Ph. Eur.* Secretariat (Annex 4), which were based on the outcome of this AGAATI study.

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