The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POSITION PAPER ON BATCH POTENCY TESTING OF IMMUNOLOGIAL VETERINARY MEDICINAL PRODUCTS

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General Remarks

The Committee for Veterinary Medicinal Products considers that in the interests of animal and human welfare only those batches of veterinary vaccines which have been shown to be in accordance with the standards of quality, safety and efficacy documented in the marketing authorisation shall be released onto the market.

In relation to batch to batch consistency of final product Directive 81/851/EC states that "In order to ensure that efficacy of the product is reproducible from batch to batch and to demonstrate conformity with specifications, batch potency tests based on *in vitro* or *in vivo* methods, including appropriate reference materials, whenever available, shall be carried out on each final bulk or each batch of finished product, with appropriate confidence limits."

Whatever batch potency test is used the Working Party stresses the need for it to be validated and shown to be a relevant indicator of the efficacy of the product and related to the efficacy claims being made for the product in the target species. The Working Party also wishes to encourage the replacement of *in vivo* batch potency tests of the finished product by standardised and validated *in vitro* tests carried out to measure the potency of the finished product as a whole. In cases where the appropriate supporting evidence is provided, assessment of the potency of a batch of the whole product may be achievable by, for example, quantifying one or more components separately *in vitro* when there is a validated method of relating this to the potency of the whole product.

In the present stage of scientific knowledge it would, however, be impossible to produce recommendations on the potency requirements and validation of a batch potency test for individual types of vaccines. Batch potency tests in line with the following general principles will be evaluated on a case by case basis. The Working Party are of the consensus that the validation of analytical methods, including statistical methods, to be used are already described in the European Pharmacopoeia. For these reasons, the Working Party have put together a list of points to be considered during the development and validation of batch potency tests.

Aspects to be considered during the development and validation of batch potency tests

- A batch potency test must be carried out on each final bulk or batch of finished product.

- The batch potency test must be a relevant indicator of the efficacy of the product and must be related to the efficacy claims being made for the product. It must be able to demonstrate that batches of product to be placed on the market will have at least the same level of efficacy (immunogenicity) as that achieved by a batch or batches of minimum potency for which adequate supporting data has been provided in the dossier submitted in support of the marketing authorisation.

- Where a European Pharmacopoeia monograph exists, the Potency test in the test section of the monograph is the reference method and sets the requirements with which all products must comply. In accordance with the General Notices of the European Pharmacopoeia, for batch potency testing alternative methods may (and usually will) be used.

- For vaccines containing living organisms the batch potency test can be determined by titration to determine whether the number of viable organisms present in a dose of vaccine is within the limits specified in the marketing authorisation on the basis of the safety and efficacy data.

- For inactivated vaccines, especially those containing an adjuvant, it may be difficult to establish a meaningful link between efficacy and the measurement of only one component (such as the antigen content) as a reliable indicator of the potency of the batch. For such products the batch potency test will

usually measure some relevant aspect of the immunogenicity of the finished product in either the target species or an appropriate laboratory animal model.

- In a majority of cases where the batch potency test involves administration of the product to either the target species or another species the method will use a single vaccination as the amnestic response to a second vaccination results in reduction of the slope of the dose regression curve.

- As a minimum, any batch potency test chosen shall be sufficiently sensitive to be able to distinguish between potent and sub-potent batches. Test linearity and maximum titre have to be taken into account also.

- The conditions needed to establish the most discriminating and reproducible dose-response relationship shall be determined. The parameters shall include volume of injection, dilution of vaccine, route of administration and number of injections. Guidance on statistical analysis can be found in European Pharmacopoeia guidance on the validation of analytical methods (Pharmeuropa special edition 1993).

- The use of both positive and negative controls may be essential in many batch potency tests.

- The use of reference preparations is one of the main ways to obtain evidence of the validity of an individual batch potency test. Such reference preparations must themselves be validated and, where international standards exist, the activity of the reference preparation relative to the international standard must be known. The potency of the product can then be expressed in terms of International Units.

- Where a batch potency test involves direct comparison with a reference batch it is preferable to determine the dose response to the reference preparation and the product. If a single dose of the product is compared with the reference batch the dose used in the test should be in the log-linear portion of the dose regression curve of the reference preparation. For such an assay, however, precision may require many readings being made.

- In many batch potency tests the reference preparation used will be a batch of product of the minimum potency for which the efficacy has been shown. Use of such a reference preparation will allow determination in each batch potency test of the minimum acceptable test value for the batch under test as well as providing evidence that the batch potency test has been carried out correctly. The exact value given for a reference preparation in a particular batch potency test will vary around the mean owing to the inherent variability of biological systems. It is important, therefore, that the accuracy and precision of the mean value for the reference preparation is determined if an acceptable range of observed values for the results of the test carried out on a batch is to be defined.

- It is important that the reference preparation in any test is as stable as possible and that its stability is monitored. Thus, on a rolling basis the value of the mean reading for the reference preparation and the variance of the mean based on data over a designated period or number of tests should be ascertained. It is also imperative that the results for the reference preparation are within the same range as those expected for batches of finished product. Shelf life of the reference preparation may be extended after the marketing authorisation is granted. A procedure should be in place to enable replacement of reference preparation in the test with an alternative reference preparation and the grounds for amendment to the pass/fail/retest criteria must be defined. The assigned value of the replacement reference will usually be allocated on the basis of multiple comparative assays with the existing reference preparation.

