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 COMPLIANCE OF VETERINARY VACCINES WITH VETERINARY VACCINE MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

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INTRODUCTION

Vaccine manufacturers, Marketing Authorisation Holders and Applicants are required to ensure that their products always comply fully with the requirements of the European Pharmacopoeia monograph. When a new European Monograph is published manufacturers must fully comply with the requirements laid down in the new monograph by the date of implementation which is determined to be the 1st of January in the year following publication at the latest. The CVMP has agreed this position in order to advise industry how best to implement any necessary changes to product tests in a timely manner in order to provide the assurance that the product meets these requirements.

As the European Community has signed the *Convention on the elaboration of a European Pharmacopoeia,* all veterinary products on the market and new products under evaluation have to comply with mandatory sections in current monographs from the implementation date. In accordance with Council Directive 81/852/EEC the current monographs of the European Pharmacopoeia shall be applicable to all substances appearing in it.

The General Notice 1, paragraph 7 of the 3rd edition of the European Pharmacopoeia states that
"... the tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative ...".

This implies that marketing authorisation holders or applicants shall change to the European Pharmacopoeia standards or validate their control procedures to demonstrate that they are equivalent in order to ensure compliance with the current standards of the monograph.

This assurance, given to Competent Authorities, means that the Marketing Authorisation Holder or the Applicant shall either re-test the reference batch using the European Pharmacopoeia methods or provide justification and, where necessary, validation data to show equivalence. The Competent Authority decides on that justification or validation.

It must be remembered that any amendment to the content of applications such as they existed at the moment the decision on the marketing authorisation has been adopted or after approval of any previous variations must be considered as a variation to the terms of a marketing authorisation in accordance with Commission Regulations (EC) Nos 541/95 and 542/95 as amended.

DEMONSTRATION OF COMPLIANCE WITH THE EUROPEAN PHARMACOPOEIA MONOGRAPH

The implications of implementation of new and modified relevant monographs to existing marketing authorisations and for applications for new vaccines have now to be considered. They are to be considered in the same way. For most vaccines, a representative batch will have to be tested to demonstrate compliance of the product with the requirements specified in the test for Potency described in the monograph. In addition, each batch will have to be tested to show compliance with the standards specified in the monograph e.g. for sterility, safety and other characteristics, such as inactivation, physico-chemical tests and requirements specific for that type of product.

Types of tests in the monographs and how they should be implemented

- Potency tests particularly may be a potential problem area; in the majority of monographs these are tests which specify vaccination and challenge of animals of the target species. If the available data on efficacy gives sufficient information and reassurances that the product would pass the current EP test if applied, then this should be sufficient. Although it is up to the applicant to show equivalence, authorities should not require a product to be re-tested except in cases of real doubt or dispute. In the case of potency tests, equivalence of a method will generally be accepted providing test conditions and selected end-points are at least similar and the accepted pass criteria for the vaccinates and controls are similar to those specified in the test in the European Pharmacopoeia.

- For batch potency tests regarding inactivated vaccines, the monographs give a suggested method, but also reference methods. The applicant or the marketing authorisation holder has to use a validated method with the pass level set with reference to a batch shown to be satisfactory in the Potency test. They should validate their potency test during development of the product and setting the pass level with reference to a representative batch shown efficacious. In the case of live vaccines, a minimum titre will have been set for the product and that will have been shown efficacious.

- Microbiological sterility and mycoplasma batch tests are standard tests required by the monograph "Biological tests" and may not need to be considered further.

- Physico-chemical batch tests are general tests required by the monograph "Vaccines for veterinary use" with product specific pass levels and may not need to be considered further.

- Identification, inactivation and safety batch tests which differ from those described in the current monograph shall be justified and validated to show equivalency, especially regarding sensitivity and specificity

CONCLUSIONS

Applicants and Marketing Authorisation Holders shall provide the necessary validation data, or justify any method and/or requirement alternative to that of the European Pharmacopoeia, in order to reassure the Committee that the product complies with the standards of the European Pharmacopoeia monograph concerned and that routine batch testing provides the necessary assurances for each batch.

