The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/CVMP/552/02-CONSULTATION

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

GUIDELINE ON

EU REQUIREMENTS FOR BATCHES WITH MAXIMUM AND MINIMUM TITRE OR BATCH POTENCY FOR DEVELOPMENTAL SAFETY AND EFFICACY STUDIES

AGREED BY IMMUNOLOGICALS WORKING PARTY	13 MAY 2002
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	12 JUNE 2002
START OF CONSULTATION	13 JUNE 2002
END OF CONSULTATION	31 DECEMBER 2002

Public

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EU REQUIREMENTS FOR BATCHES WITH MAXIMUM AND MINIMUM TITRE OR BATCH POTENCY FOR DEVELOPMENTAL SAFETY AND EFFICACY STUDIES

INTRODUCTION

It is stated in Directive 2001/82/EC that -

a) The dose to be used [in safety studies] shall be that quantity of the product to be recommended for use and containing the maximum titre or potency for which the application is submitted. (Title II, Part 7 B. General Requirements, paragraph 2)

b) The dose to be used [in efficacy studies] shall be that quantity of the product to be recommended for use and containing the minimum titre or potency for which the application is submitted. (Title II, Part 8 B. General Requirements, paragraph 6)

These requirements are repeated in the general mammalian vaccine guidelines (GRIMV and GRLMV), in the relevant sections of the European Pharmacopoeia monograph Vaccines for Veterinary Use and in a number of specific monographs (e.g. Feline Viral Rhinotracheitis Vaccine, Living).

The principles underlying these requirements are widely accepted, namely that the safety and efficacy of veterinary vaccines are profoundly affected by, among other factors, the quantity and quality of the antigen present, and that for both aspects it is important to evaluate the 'worst case' scenario. In the case of safety this relates to the administration of the greatest possible amount and strength of antigen and, in the case of efficacy, that the minimum possible amount of antigen likely to be contained in the vaccine will still induce the required degree of protection. Difficulties frequently arise when manufactures attempt to apply these clear principles in practice, particularly for inactivated immunological products.

SCOPE OF THE PAPER

This paper discusses how best these principles can be put into practice, analyses the reasons why it might sometimes be difficult to comply with these requirements completely, indicates the situations in which Licensing Authorities are likely to be sympathetic to deviations from the requirements, and explains the kinds of justification for deviation that would be considered acceptable.

RATIONALE

1. General points

The biological nature of IVMPs leads to some unavoidable batch to batch variation in production. Manufacturers, therefore, set limits rather than absolute parameters for most processes.

The test methods available to assay the product during and at the completion of production are also subject to biological variability. They often only provide indicators of the quality, quantity and the reproducibility of the product batches rather than precise measures.

The definition of maximum and minimum potency or titre is only meaningful if there can be confidence in the tests used to measure these parameters. Adequate validation is essential to ensure that the results of the assays accurately reflect the amount, titre, or potency of the ingredient measured and to indicate the limitations on the accuracy of the measurements to be expected from the test used. This applies equally well to in-process control tests used to measure antigen prior to blending or inactivation as it does to final batch potency tests. All these factors will influence the confidence that the regulatory authorities can be given that the tests will be capable of accurately determining the titre or potency of the product and the extent to which the value given for the potency reflects the actual or likely potency of the batch.

2. Live vaccines

For many live vaccines, it is possible to carry out a titration of the living vaccinal organisms with a reasonable level of precision. It is normal for the titre per dose to vary from batch to batch and to decrease over the shelf-life. Thus, the quantity of active substance administered per dose will vary. As both safety and efficacy are frequently profoundly affected by the dose of a live organism, and as it is usually relatively easy to measure the organism in the vaccine, there is generally little reason why vaccines of minimum and maximum potency cannot be used for appropriate studies.

3. Inactivated vaccines

For inactivated vaccines, in-process test are carried out to determine the quantity of antigen for blending but the variables involved in production and testing will usually result in some variability in quality and quantity of antigen input.

The safety and efficacy of an inactivated vaccine usually depend on the content and the quality of the active substance (antigen), on the adjuvant, and on the way the two react together. In cases where vaccines are formulated with a variable or invalidated antigen input, potency tests on the final product usually measure an immune response in animals. This response depends on all of the above factors, and the animals themselves introduce another source of variability. Thus, when requiring a batch of minimum potency for efficacy trials, knowledge alone of the amount of antigen used in formulation is only sufficient when there is a fully validated antigen quantification assay that has been adequately correlated with efficacy in the target species (covered in more detail in the Section 'Practical Consideration').
The need to consider potency for efficacy studies is reinforced by the fact that the value obtained for the batch potency per dose of an inactivated vaccine will vary from batch to batch, and the batch potency will usually decrease over the shelf-life.

PRACTICAL CONSIDERATIONS

1. General points

i) The minimum titre or batch potency is that stated to be present throughout the shelf -life of the product.

ii) The maximum titre or batch potency is that expected as the maximum at release of each batch of product.

iii) The proposed maximum and minimum titres or batch potencies for the active substances in the product should correspond to those that have been shown safe and efficacious.

iv) The aim of the safety and efficacy studies is to evaluate an IVMP, which is the result of a complex process of production. Any manipulations performed on the final product to obtain a maximum or a minimum titre could lead to a product that does not fully reflect the production process described in the dossier. Manipulations should therefore be kept to an absolute minimum. When considered necessary, the nature of the manipulations should be clearly indicated and the need for them fully justified.

v) Provided that laboratory tests have adequately assessed the safety and efficacy of a vaccine under experimental conditions using vaccines of maximum and minimum potency or titre respectively, a single batch of vaccine could be used to assess both safety and efficacy under field conditions. In these cases, it may be reasonable for the batch to be of intermediate titre or potency and to be typical of a routine production batch.

2. Live vaccines

a) Single component live vaccines
High and lower titred batches are often produced and are available for study and, as stated previously, there is rarely a justification for not using batches of an appropriate titre. For freeze-dried vaccines, if the pilot scale batches are not sufficiently close to the minimum and maximum titres, which will be present in full scale production batches, it might be acceptable for the titre per dose of the product administered to be adjusted. For example the freeze-dried pellet could be reconstituted in slightly more or less diluent. This would only be appropriate where a simple solvent such as water or saline was used to reconstitute the pellet and would not be appropriate if the pellet is reconstituted in a complex diluent, such as one containing an adjuvant or other immunological active substance. In all cases of manipulations such as this, an explanation and suitable justification should be given.

b) Combined vaccines
Due to the complex composition of combined vaccines, there is more often a justification for not matching exactly the requirements of the Directive in terms of the potency or titre of particular components used in studies.
Ideally, for safety testing, the batch would contain at least maximum titres of all active substances. It is accepted, however, that this may be difficult to achieve in any one batch. Nevertheless, sufficient justification must be provided, perhaps in the form of multiple trials with different components at maximum titre, that each of the components are safe at the maximum titre proposed for the product.
For efficacy testing, it is important that, in any trial, the titre of the active substance under study is at or below minimum titre. Thus, if necessary, different batches can be used in different studies. Since, to minimise the use of animals, the duration of immunity (DOI) studies will require study of all components, the batch used for this work should contain titres as close to the proposed minimum for all components as can be justified. As indicated in the Note for Guidance on Field Trials for Veterinary Vaccines (EMEA/CVMP/852/99), in the case of field studies it may be acceptable to use a batch of vaccine produced according to the method described in the marketing authorisation that is representative of those found in routine production and that is therefore of a titre or potency intermediate between the permitted maximal and minimal values.

3. Inactivated vaccines

a) Single component vaccines

In general, there is little justification for a company not to test high and low potency batches of single component vaccines. The minimum potency specification is usually set based on challenge dose titration studies and the maximum potency on adverse reactions obtained in specific safety studies, both carried out in the target animal. The batch potency test is usually validated as a separate exercise to ensure that there is a statistically valid relationship between potency in the batch potency test and efficacy in the target species. This validation exercise will provide information on the range of batch potency values obtained for the batches produced so far and the extent to which the measured differences in potency of batches are likely to be actual differences.

Variable or invalidated antigen input

Where there is a range of antigen input that may be used in production, then batches selected for the safety and efficacy studies should be those, which have maximum and minimum antigen content respectively.

For some inactivated vaccines there is no validated quantification of the amount of antigen added at the blending step and therefore final vaccines can have a range of antigen input which is poorly defined. The potency test for such products is usually an *in vivo* test followed by measurement of a serological response. Acceptance limits for the potency test are usually set by reference to the results of batches used in the safety tests (maximum limit) and the efficacy tests (minimum limit) and therefore, by default, the tests will have been performed with batches of the relevant potency.

Fixed and validated antigen input

For some inactivated vaccines the manufacturer may use a validated method for quantification of antigen at the blending stage and will blend to a fixed quantity of antigen (within the limits of quantification of the assay used). In such cases the manufacturer may choose to blend vaccines with a greater or lesser amount of antigen for safety or efficacy trials but would have to justify how such vaccines could be considered to comply with the requirement that the vaccines used in safety and efficacy trials must contain a 'quantity of product to be recommended for use'. If an adequate justification can be provided and the results of such trials are satisfactory then any batch with an intermediate amount of antigen should be considered satisfactory.

More likely, the manufacturer will use a batch of fixed antigen content and then seek to justify that the potency of the batch is irrelevant as the vaccine is blended to constant antigen content. This justification can be accepted provided that, during validation of the potency test, a correlation has been shown between antigen content and the result of the potency test and the result of potency test of the batches used for safety and efficacy trials is within the acceptance limits set for a batch of the defined, fixed antigen content.

It is always important to include in the dossier a justification for the choice of batches actually used in the studies and the extent to which they meet the requirements. This could include, for example,

a) a reference to the use of high or low antigen input at blending or the fact that the blending is always to an exact titre;
and
b) the extent to which the batch used is representative of batches with minimum or maximum batch potency.

For adjuvanted vaccines, it would not be acceptable to adjust the potency by any form of diluting the vaccine as this will result in a vaccine that is not representative of the product to be marketed. Similarly, adjusting the volume of the dose administered would not be acceptable.

b) Combined vaccines
It is recognised that this is the type of vaccine for which it is, in practice, the most difficult to achieve compliance with the requirements. However, as with single component vaccines, for safety and efficacy testing, batches with maximum and minimum antigen contents should be blended wherever possible.

Batches used in safety studies should always contain maximum batch potencies of all components. For vaccines blended with a range of antigen input, it should be relatively straightforward to blend a vaccine with the maximum or minimum amount of each component. However, for vaccines blended to a consistent antigen content but for which the potency of the antigen content might vary, it can be extremely difficult to blend a single batch with all components at maximum or minimum potency. Batches as close to the requirements as possible should be used and any deficiencies should be justified. For efficacy studies, particularly laboratory studies, it is frequently necessary and usually acceptable, to use different batches for different studies, and to ensure that the component under study is always at minimum potency in the batch used. For safety studies, it may be acceptable for some of the components not to be at maximum potency, provided it is clear elsewhere in the dossier that safety is not significantly related to the potency value for the component concerned. As discussed previously, to minimise the use of animals, DOI studies will require study of all components and the batches used for this work should be representative of batches containing minimum batch potencies for all components.

As for single component inactivated vaccines, a justification for the choice of batches actually used should be given, indicating the extent to which they meet the requirements.

