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Guideline on data requirements for removing the target animal batch safety test for immunological veterinary medicinal products in the EU

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Table of contents

Executive summary

This guideline outlines the data requirements to be submitted by the marketing authorisation holder in order to waive the target animal batch safety test for the release of a batch of this product onto the market.

1. Introduction (background)

The European Pharmacopeia (Ph. Eur.) General monograph, Vaccines for Veterinary Use (0062), was revised in January 2004 (Supplement 4.6, Ph. Eur., 4th Edition) to state 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 if the competent authority considers that the changes introduced could adversely affect product safety. The requirements laid out in this guideline apply equally to both well established products and those that have been recently authorised. In the light of the changes to the Ph. Eur. monograph, the CVMP has developed this guideline for harmonising the data requirements for removing the target species safety test. The ability to waive this requirement relies, at least in part, on the assurance of product safety that is given by the current EU requirement for pre-authorisation safety tests (single dose, overdose, repeat dose). This guideline will need to be reviewed should these requirements be amended in the Ph. Eur. or as a result of international harmonisation.

2. Definitions

Final Batch

A collection of closed, final containers or other final dosage units that are expected to be homogeneous and equivalent with respect to risk of contamination during filling or preparation of the final product. The dosage units are filled, or otherwise prepared, from the same final bulk vaccine, freeze-dried together (if applicable) and closed in one continuous working session. They bear a distinctive number or code identifying the final batch. Where a final bulk vaccine is filled and/or freeze-dried on several separate sessions, there results a related set of final batches that are usually identified by the use of a common part in the distinctive number or code; these related final batches are sometimes referred to as sub-batches, sub-lots or filling lots.

Final bulk vaccine

Material that has undergone all the steps of production except for the final filling. It consists of one or more monovalent pooled harvests, from cultures of one or more species or types of micro-organism, after clarification, dilution or addition of any adjuvant or other auxiliary substance. It is treated to ensure its homogeneity and is used for filling the containers of one or more final lots (batches).

Batch safety test

A safety test carried out on every batch of product to demonstrate the safety of the batch in the target species for which the product is intended. Where several batches are prepared from the same final bulk, the safety test is carried out on the first batch and then omitted for further batches prepared from the same final bulk.

Using at least the recommended route of administration posing the greatest risk, each batch of vaccine shall be shown to be safe in at least two susceptible animals from the most sensitive target species for which the vaccine is recommended.

3. Points to consider for removing the batch test for target animal safety

In general it is sufficient to evaluate existing information which is available from routine batch quality control and pharmacovigilance data, without the need for any additional supplementary studies. The data which should be presented to support such an application are presented below. However, this should not be taken as an exhaustive list, and should in all cases be accompanied by a summary report which brings together all of the data presented in terms of an overall assessment of the risk that waiving the requirement will represent.

3.1. The characteristics of the product and its manufacture

Directive 91/412/EEC covers the principles and guidelines of Good Manufacturing Practice (GMP) and provides assurance that products placed on the market place have been manufactured in a consistent and suitable manner. However, because of the inherent variability of biological products, there is a requirement for final product testing to provide further assurance that the product has been manufactured to the appropriate specifications. The target animal batch safety test on final product provides some assurance that the product will be safe in the target animal species even when administered at an overdose using the route of administration most likely to demonstrate a safety concern.

If the batch safety test is to be deleted as a final product test, a summary report should be provided which would encompass the inherent variability of manufacture of the product, the intrinsic safety margin and the validation which was undertaken to provide the necessary assurance that the product would always be manufactured to an acceptable level of quality and safety.

This would include the characteristics of the product, taking account of whether it has live and/or inactivated viral and/or bacterial components and for live components any residual virulence has been shown to be safe. The type of excipients, adjuvants and preservatives incorporated in the final formulation should be considered.

The applicant should also take account of the range of specifications for the manufacture of the product and how the extremes of the ranges and variability of the final formulation may influence the safety profile of the final product. In exceptional circumstances, where the safety threshold of the product is narrow, the applicant should justify that any issues related to batches at the limits of these parameters could be detected in the absence of the batch safety test. An example of this would be to examine the target ranges of endotoxin, which may be permitted in the final formulation, and how slight alterations in production conditions may influence the subsequent levels of endotoxin and the impact this may have on the safety profile of the resulting formulation.

For those circumstances when *in vivo* batch tests are conducted in the target species for reasons other than the target animal safety test, it is recommended that manufacturers use these tests to gain data of the safety of the vaccine in the target species.

3.2. Information available on the current batch safety test

Batch data should be submitted on at least 10 consecutive batches from separate final bulks, unless justified. These data may be submitted in the form of a table that lists the results for all finished product tests to demonstrate that the batches consistently met the agreed specifications and also details the antigen bulks used. The applicant should examine the variability of the local and systemic reactions observed in the batch safety test results and the nature of these reactions in relation to those observed in any developmental studies submitted in support of the marketing authorisation. The conduct of the trial shall be in accordance with the Ph. Eur. requirements in operation at the time when the tests were performed. There should be a thorough examination of any batches that have failed the batch safety test and this information, along with an explanation as to the reasons for failure, should be submitted to the regulatory authorities. Information on the number of years the product has been marketed in the EU should be provided.

3.3. Pharmacovigilance data

A satisfactory pharmacovigilance system should have been in place over the period during which the batches for which data are submitted were on the market.

Pharmacovigilance data to support the removal of the batch safety test should be provided. Marketing authorisation holders should follow the Note for Guidance for veterinary pharmacovigilance for marketing authorisation holders. The most recent Periodic Safety Update Report (PSUR) for the product should be submitted in the variation application to support the removal of the batch safety test. The summary report should include an overall assessment of the product, which would include taking account of the number of batches manufactured, the number of years the product has been on the market, the number of doses sold and the frequency and seriousness of any reactions relating to the safety in the target species and any investigations into the likely causes of these events.

3.4. Other data

Applicants should summarise the variation applications that have been submitted during the life of the marketing authorisation and any effects these changes may have had on the quality and safety profile of the product in the different categories of animals to which the product is given.