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Draft

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Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL50 (BIOLOGICALS: TABST)
November 2011
For consultation at Step 4

TESTING HARMONISATION OF CRITERIA TO WAIVE TARGET ANIMAL BATCH SAFETY TESTING FOR INACTIVATED VACCINES FOR VETERINARY USE

Recommended for Consultation
at Step 4 of the VICH Process
on 17 November 2011
by the VICH Steering Committee

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1. INTRODUCTION

Submission of batch safety test data from target or laboratory animals is a requirement for batch release of immunological veterinary medicinal products (IVMPs) in the regions participating in the VICH. The VICH Steering Committee has decided to aim at harmonization of the batch safety tests across the regions in order to minimize the need to perform separate studies for regulatory authorities of different countries. However, due to the great divergence in requirements between the regions it was concluded to adopt a phased approach with the first step to harmonize the criteria on data requirements for waiving of the target animal batch safety test (TABST) for inactivated vaccines in regions where it is required.
This guideline has been developed under the principle of VICH and will provide unified criteria for government regulatory bodies to accept waivers for TABST. The use of this VICH guideline to support a similar approach for products for local distribution only is strongly encouraged but is up to the discretion of the local regulatory authority. Furthermore, it is not always necessary to follow this guideline when there are scientifically justifiable reasons for using alternative approaches.

Global implementation of TABST waiver reduces the use of animals for routine batch release and should be encouraged.

1.1. Objective of the guideline

The objective of this guideline is to provide internationally harmonized recommendations for criteria on data requirements to waive target animal batch safety testing of inactivated immunological veterinary medicinal products (IVMPs) in regions where it is required.

1.1.1. Background

Most batch safety tests in laboratory and/or target animals on final product can be considered as general safety tests. They apply to a broad group of IVMPs and should provide some assurance that the product will be safe in the target species, i.e. it should reveal “abnormal local or systemic reactions” (European Pharmacopoeia) or “unfavorable reactions attributable to the biological product ...” (Title 9. United States Code of Federal Regulations) or “no abnormal changes” (Minimum Requirements for Veterinary Biological Products under the Pharmaceutical Affairs Law in Japan).

Over the last two decades, the relevance of batch safety tests has been questioned by representatives of regulatory authorities and vaccine manufacturers (Sheffield and Knight, 1986; van der Kamp, 1994; Roberts and Lucken, 1996; Zeegers et al., 1997; Pastoret et al., 1997; Cussler 1999; Cussler et al., 2000; AGAATI, 2002; Coopers, 2008). Particularly, the introduction of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP; OECD 1998) or similar quality systems appropriate to regional requirements into the manufacture of vaccines has greatly increased the consistency of the batches produced and hence their safety and quality. This has also influenced the attitude towards quality control from the traditional batch control for IVMP (based in major parts on *in vivo* testing) towards putting more emphasis on documentation of consistency of production which is mostly based on *in vitro* technologies (Lucken, 2000, Hendriksen et al. 2008, de Mattia et al, 2011).

In reviewing the data requirements in the different VICH regions and comments received at the 21st VICH Steering Committee meeting it became apparent that the approach to the batch safety testing and consequently the test procedures required differ considerably between the regions. This makes harmonization of test requirements and test performance a difficult and time-consuming task.

It was therefore decided as a first step to harmonize the criteria to waive the target animal batch safety tests across the regions and to start with the development of a VICH guideline for inactivated IVMPs. It is foreseen that should this prove successful the scope may be extended to live vaccines in the future.

2. GUIDELINE

2.1. Scope

This guideline is limited to the criteria on data requirements for waiving target animal batch safety tests (TABST) of inactivated immunological veterinary medicinal products.

2.2. Regional Requirements

2.2.1. General batch safety testing

Currently the following testing procedures (Table 1) are required for batch safety testing of inactivated IVMPs covered by this guideline:

Table 1:

VICH region	Requirements	Remarks
Europe: - European Pharmacopoeia: General chapter 5.2.9. Safety of batches of veterinary vaccines and immunosera; - General monograph on Vaccines for Veterinary use (0062), and specific monographs	target species (2 mammals, 10 fish, 10 birds), 2x dose, recommended route, minimum 14 d observation	can be waived provided that at least 10 consecutive batches from separate final bulks had been tested and product complies with the test
USA: - 9CFR – General requirements for inactivated bacterial vaccines (113.100)	mice (113.33) or – if inherently lethal to mice then guinea pig (113.38) – if poultry vaccines then poultry – if fish vaccines or other aquatic species, then fish	

	– if reptilian vaccines then reptiles 113.38 – 2 guinea pigs, 2 ml im or sc, 7 d observation	
General requirements for killed virus vaccines (113.200)	guinea pigs (113.38) mice (113.33b) 113.38 – 2 guinea pigs, 2 ml im or sc, 7 d observation 113.33a – 8 mice, 0.03 ml ic, 7 d observation; 8 mice, 0.5 ml ip, 7 d observation	not for poultry vaccines
Japan: Minimum Requirements for Veterinary Biological Products under the Pharmaceutical Affairs Law in Japan	a) Target Species Mammalian: 2 to 4 mammals, 1 to 5x dose, approved route, 10 to 14 d observation Birds: 10 birds, 1x dose, approved route, 2 to 5 weeks observation Fish: 15 to 120 fishes, 1x dose, approved route, 2 to 3 weeks observation b) The abnormal toxicity test: guinea pig: 2 guinea pigs, 5 ml ip, 7 d observation mice: 10 mice, 0.5ml ip, 7 to 10 d observation c) Toxicity limit test: mice: 10 mice, 0.5mL ip, 7 d observation guinea pig: 5 guinea pigs, 5mL ip, 7 d observation	

2.2.2. Other relevant requirements

2.2.2.1. Quality Systems

Good Manufacturing Practices (GMP) and similar quality systems have been established in VICH countries/regions to cover the manufacture and testing of medicinal products including veterinary medicinal products. These quality systems provide assurance that products placed on the market have been manufactured in a consistent and suitable manner.

2.2.2.2. Pharmacovigilance

The VICH process increasingly includes pharmacovigilance (post-marketing surveillance of medicines) in the veterinary field and the harmonization of the requirements and performance. This provides for early detection of safety problems associated with the inconsistent quality of a vaccine in the field. Thus, pharmacovigilance provides extra information about the product's safety that cannot always be obtained in the TABST.

2.3. Data requirements for waiving of target animal batch safety tests

2.3.1. Introduction

The TABST may be waived by the regulatory authority when a sufficient number of consecutive production batches have been produced and found to comply with the test, thus demonstrating consistency of the manufacturing process.

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 by the manufacturer to support an application to waive TABST are presented below. However, this should not be taken as an exhaustive list, and in all cases applications for waiving the TABST should be accompanied by a summary of all the data and a conclusion on the assurance of the product's safety being maintained.

In exceptional cases, significant changes to the manufacturing process may require resumption of target animal batch safety testing to re-establish consistency of the safety profile of the product. The occurrence of unexpected adverse events or other pharmacovigilance problems which could be avoided using a TABST may also lead to the resumption of the test. For products with an inherent safety risk, it may be necessary to continue to conduct the TABST on each batch.

2.3.1.1. The characteristics of the product and its manufacture

The manufacturer should demonstrate that the product is manufactured following the quality principles, i.e. the product has been manufactured in a consistent and suitable manner.

For those circumstances when *in vivo* batch tests are conducted in target animals for reasons other than the target animal safety test (e.g. potency tests) and these tests include the collection of safety information (e.g. on mortality), it is recommended that manufacturers use these tests to gain additional data of the safety of the vaccine in the target species.

2.3.1.2. Information available on the current batch safety test

The manufacturer should submit batch protocol data for a sufficient number of consecutive batches to demonstrate that safe and consistent production has been established. Without prejudice to the decision of the competent authority in light of the information available for a given vaccine, test data of 10 consecutive batches is likely to be sufficient for most products. The manufacturer should examine the variability of the local and systemic reactions observed in the TABST results and the nature of these reactions in relation to those observed in any developmental studies submitted in support of the registration or licensure of the product. The manufacturer should provide a summary and discussion of the findings.

The conduct of the TABST shall be in accordance with the regional requirements in operation at the time when the tests were performed. There should be a thorough examination of any batches that have failed the TABST in the time period during which the agreed number of consecutive batches have been tested. This information, along with an explanation as to the reasons for failure, should be submitted to the regulatory authorities.

2.3.1.3. Pharmacovigilance data

A pharmacovigilance system in accordance with the VICH Guidelines, where available, should have been in place over the period during which the batches for which data are submitted were on the market. Safety information from pharmacovigilance and TABST are by nature different but complement each other.

Available pharmacovigilance data to demonstrate the consistent safe performance of the vaccine in the field should be provided using recent Periodic Safety Update Reports for the relevant time period.

2.3.2. Procedure for waiving the target animal batch safety test

A report should provide an overall assessment of the consistency of the product's safety and would include taking into account 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 adverse reactions in the target species and any investigations into the likely causes of these events.

3. GLOSSARY

Good Laboratory Practices (GLP): A standard for the design, conduct, monitoring, recording, auditing, analysis, and reporting of non-clinical studies. Adherence to the standard provides assurance that the data and reported results are complete, correct and accurate, that welfare of the study animals and the safety of the study personnel involved in the study are ensured, and that the environment and the human and animal food chains are protected (OECD, 1998).

Good Manufacturing Practices (GMP): Is part of a quality system covering the manufacture and testing of medicinal products including veterinary medicines. GMPs are guidelines that outline the aspects of production and testing that can impact the quality of a product standard assuring the quality of production processes and the production environment during the production of a medicinal product.

Immunological veterinary medicinal product (IVMP): Any veterinary medicinal product administered to animals in order to produce active or passive immunity or to diagnose the state of immunity

Production Batch: A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.
Note To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

TABST: Target Animal Batch Safety Test; Safety test in target animals which is performed as a routine final product batch test for all IVMPs or a product group such as inactivated viral vaccines.

Target Animal: The specific animal species, class and breed identified as the animal for which the IVMP is intended for use.

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