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VICH GL59 Harmonisation of criteria to waive laboratory animal batch safety testing for vaccines for veterinary use

Draft

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

VICH GL59 (BIOLOGICALS: LABST VETERINARY VACCINES)
October 2019
For consultation at Step 4

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

Recommended for Consultation at Step 4 of the VICH Process
in October 2019
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group and will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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1. INTRODUCTION

Submission of batch safety test data from target or laboratory animals is a requirement for batch release of veterinary vaccines in several regions participating in the VICH[1]. The VICH Steering Committee has proposed to harmonize the batch safety tests across the regions in order to minimize the need to perform separate studies for regulatory authorities of different countries. The initial steps focused on the target animal batch safety test (TABST) and adoption of two guidelines harmonizing criteria for waiving the TABST for inactivated (VICH GL50(R)) and live vaccines (VICH GL55).

This guideline addresses laboratory animal batch safety tests (LABST) and harmonization of criteria for waiving it in regions where it is required.

The guideline has been developed under the principle of VICH and will provide unified criteria for government regulatory bodies to accept waivers for LABST. The use of this VICH guideline to support a similar approach for products for local distribution only is strongly encouraged but is at 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 LABST waiver reduces the use of animals for routine batch release and should be encouraged in the light of VICH's commitment to replacement, reduction and refinement (3Rs).

1.1. Objective of the Guideline

The objective of this guideline is to provide internationally harmonized recommendations for criteria on data requirements to waive the LABST for veterinary vaccines in regions where it is required.

1.1.1. Background

Most batch safety tests in laboratory animals on the final product can be considered as general safety tests. They apply to a broad group of veterinary vaccines and should provide some assurance that the product will be safe in the target species, i.e. it should reveal “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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics* in Japan) or, as formerly required in Europe, “abnormal local or systemic reactions”.

Over the last decades, the relevance of LABST has been questioned by representatives of regulatory authorities and vaccine manufacturers (Krämer et al., 1996; Pastoret et al., 1997; Schwanig et al., 1997; Kulpa-Eddy et al., 2011; Schutte et al., 2017). Particularly, the introduction of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP; OECD, 1998) or similar quality systems appropriate to regional requirements as well as a seed lot system into the manufacture of vaccines has greatly increased the

[1] In the EU, neither TABST nor the abnormal toxicity test (one type of LABST) are required (see section 2.2.1)

consistency of the batches produced and hence their quality and safety. This has also influenced the attitude towards quality control from the traditional batch control for veterinary vaccines (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).

Following the finalization of VICH GL50 and VICH GL55 concerning TABST for inactivated and live veterinary vaccines, this guideline describes the criteria to waive the LABST for veterinary vaccines.

2. GUIDELINE

2.1. Scope

This guideline is limited to the criteria on data requirements for waiving LABST for veterinary vaccines.

2.2. Regional Requirements

2.2.1. Laboratory animal batch safety testing

Significant variations are evident in regional requirements; however, these are more related to the products for which a LABST is stipulated than in the test design for a non-specific safety test. Other tests in laboratory animals may exist for certain classes of products pertaining to a specific safety aspect of a vaccine (e.g. residual toxicity of a bacterial toxin in bacterial and/or toxoid vaccines, residual live virus in rabies vaccines). These tests are not described below but may benefit of the same system (see paragraph 2.3.1) depending on adapted risk assessment.

Europe

The abnormal toxicity test in laboratory animals (mice and guinea pigs) is no longer required in Europe since 1996 (Krämer et al, 1996; Schwanig et al, 1997), and therefore not specified for safety testing of veterinary immunologicals in the European Pharmacopoeia Monograph 62 on vaccines for veterinary use (European Pharmacopoeia, 2019).

United States

Veterinary biologicals must meet certain basic criteria including safety requirements: the product must be safe in the target species and, if live, in species exposed to shed organisms. In addition, safety tests in mice or guinea pigs are required. General requirements for live and killed bacterial vaccines, live and killed viral vaccines and antibody products as well as the detailed requirements for each type of product are described in Title 9 CFR Part 113.

- *Live bacterial and live viral vaccines:* Safety tests for mammalian vaccines are carried out in mice or guinea pigs.
- *Inactivated bacterial vaccines:* Safety tests for mammalian vaccines are carried out in mice or, if lethal for mice, in guinea pigs.

- *Inactivated viral vaccines:* Safety tests for mammalian vaccines are carried out in mice and guinea pigs.
- All avian and aquaculture vaccines require target animal batch safety testing and no laboratory animal testing is involved.

Japan

In Japan, medicinal products that are exclusively used for animals, including veterinary biologicals, are under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries, and ensuring their quality, efficacy and safety is included in the *Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics* (PMD Act). Under the PMD Act, "Minimum Requirements for Veterinary Biological Products (Japan MRVBP; 2002)" stipulates "the lot safety test" in the target animal species for all vaccines, with the exception of inactivated vaccines for cattle and horses, although it varies depending on the characteristics of vaccine concerned. The specification of the lot safety testing for the target animals are also laid down in MRVBP. It should be noted that the term "lot" is commonly used instead of "batch".

In addition to safety tests in the target animal species, abnormal toxicity test and maximum toxicity limit confirmation test using mice and guinea pigs are carried out in all vaccines for dogs, cats and horses, and in some vaccines for cattle and pigs.

For avian vaccines, only safety tests in the target animal species are carried out.

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. Seed lot system

The establishment of a seed lot system, subject to quality and manufacturing controls, provides further assurance of the consistent production of vaccine batches and resulting batch quality.

2.2.2.3. 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 LABST.

2.3. Data Requirements for Waiving of Laboratory Animal Batch Safety Tests

2.3.1. Introduction

The LABST may be waived by the regulatory authority when a sufficient number of production batches have been produced under the control of a seed lot system 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 LABST are presented below. However, this should not be taken as an exhaustive list, and in all cases applications for waiving the LABST 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 laboratory 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 LABST may also lead to the resumption of the test.

For products with an inherent safety risk (e.g. residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines, residual live virus in rabies vaccines or other vaccines containing an agent of public health concern), it may be necessary to continue to conduct the LABST on each batch or apply a different system for waiving LABST considering level of risk and control measures.[2,3]

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.

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 batches (or a minimum of 5 batches if 10 batches are not manufactured within 3 years) is likely to be sufficient for most products. The data should be obtained from consecutively tested batches from different vaccine bulks. The manufacturer should examine the variability of the local (if applicable) and systemic

[2] In Europe, specific safety tests may already (e.g. for residual live rabies virus in mice) or may in future (e.g. residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines) be omitted on the final batch when tested at the antigen level.

[3] Based on data collected from LABST testing in Japan and USA in preparation of this guideline, most of the vaccines show no batch-dependent abnormal toxicity; however, a few products show inherent batch-dependent safety risk which might be due to residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines.

reactions observed in the LABST results and the nature of these reactions in relation to those observed in any developmental studies in laboratory animals submitted in support of the registration or licensure of the product.

Generally, data from LABST of combined vaccines may be used to waive the LABST of vaccines containing fewer antigen and/or adjuvant components provided the remaining components are identical in each case and it is only the number of antigens and/or adjuvant which has decreased. For example, LABST data from a combination product can be sufficient to waive LABSTs for all the fallout products. The manufacturer should provide a summary and discussion of the findings.

The conduct of the LABST 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 LABST 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 LABST 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.

Where there exists a system for post-marketing re-examination of field safety data for new veterinary vaccines, such data should also be considered alongside the pharmacovigilance data.

2.3.2. Procedure for waiving the laboratory 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.

Laboratory Animal Batch Safety Test (LABST): General safety test in laboratory animals which is performed as a routine final product batch test for veterinary vaccines, in regions where it is required.

Laboratory Animal: The term "laboratory animal" refers in the context of the LABST to guinea pigs and mice.

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.

Seed Lot System: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

Target Animal Batch Safety Test (TABST): Safety test in target animals which is performed as a routine final product batch test for all inactivated and/or live veterinary vaccines.

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

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