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at Step 4

GUIDELINE ON TARGET ANIMAL SAFETY FOR VETERINARY LIVE AND INACTIVATED VACCINES

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VICH GL 44 (TARGET ANIMAL SAFETY) - BIOLOGICALS

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For consultation at Step 4 - Draft 1

TARGET ANIMAL SAFETY FOR VETERINARY LIVE AND INACTIVATED VACCINES

Recommended for Consultation

at Step 4 of the VICH Process

on 6 August 2007

by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group and is 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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Table of Contents

1. INTRODUCTION

Submission of target animal safety (TAS) data is a requirement for the registration or licensure of veterinary live and inactivated vaccines in the regions participating in the VICH**.** International harmonization will minimize the need to perform separate studies for regulatory authorities of different countries. Appropriate international standards will reduce research and development costs by avoiding, when possible, duplication of TAS studies. Animal welfare will benefit because fewer animals will be needed by eliminating repetition of similar studies in each region.

This guideline has been developed under the principle of VICH and will provide a unified standard for government regulatory bodies to facilitate the mutual acceptance of TAS data by the relevant authorities. The use of this VICH guideline to support registration of a product 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.

1.1. Objective

This guideline establishes agreed criteria and requirements for the conduct of studies that evaluate the safety of final formulation of veterinary live and inactivated vaccines (investigational veterinary vaccines, IVVs) to be marketed for use in target animals.

1.2. Background

The VICH TAS Working Group was formed to develop an internationally harmonized guideline outlining regulatory requirements for the registration of IVVs in the regions participating in the initiative. By their nature, guidelines address most, but not all possibilities. General principles are included in this guideline to aid in the development of TAS study protocols.

It is important to emphasize that the international acceptance of data remains a fundamental principle for VICH.

1.3. Scope

This guideline is intended to cover safety studies of IVVs including genetically engineered products used in the following species: bovine, ovine, caprine, feline, canine, porcine, equine and poultry (chickens and turkeys). This document does not cover TAS studies conducted as part of post-approval batch release requirements. Minor species may be exempted from this requirement for local registration. The guideline will not provide information for the design of TAS studies in other species including aquatic animals. For other species, TAS studies should be designed following local guidance. Additional requirements may apply to the genetically engineered product according to the region in which authorization is sought. Immune modulators are not considered in this guideline. During development, animal safety shall be evaluated in the target animal. The purpose of the evaluation is to determine the safety of the dose of the vaccine proposed for registration. The study is therefore limited to the health and welfare of the target animals. It does not include evaluation of food safety or environmental safety including impact on human health.

The guideline is a contribution towards international harmonization and standardization of methods used for evaluation of target animal safety of IVVs. The guideline is provided to aid sponsors in preparing protocols for TAS studies conducted under laboratory conditions and in related field studies (which use a larger number of animals). All studies may not be needed. Additional studies not specified in this document and necessary to investigate specific safety concerns of the vaccine in the target animal may be necessary for certain IVVs. Therefore, specific additional requirements may be determined by communication between the sponsor and the regulatory authority.

Reversion to virulence is dealt with in a separate VICH guideline (GL 41).

1.4. General Principles

The specific information required to demonstrate target animal safety of an IVV depends upon factors such as proposed usage regimen and dose, type of IVV, nature of adjuvants, excipients, claims, previous use history of similar product, species, class, and breed.

Generally, the data from safety tests on combined vaccines may be used to demonstrate the safety 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. In some regions, this approach may not apply to field safety studies. In this case, each combination of antigens/adjuvant in the final formulation intended to be registered has to be tested.

Adverse events must be described and included in the final report and determination of causality for the adverse event attempted.

1.4.1. Standards

TAS studies done under laboratory conditions should be performed and managed in accordance with the principles of Good Laboratory Practices (GLP), for example the Organization for Economic Co-operation and Development (OECD), and field safety studies should be conducted in conformity with the principles of VICH Good Clinical Practices (GCP).

1.4.2 Animals

The animals should be appropriate for the purpose of the test with regard to species, age and class for which the IVV will be used. Treated and control animal (when used) are managed similarly. The environmental conditions of the groups should be as similar as possible. Housing and husbandry should be adequate for the purpose of the study and conform to local animal welfare regulations. Animals should be appropriately acclimatized to the study conditions. Appropriate prophylactic treatment should be completed before the initiation of the study. Reduction or elimination of suffering during the study is essential. Euthanasia and necropsy of moribund animals is recommended.

1.4.3. IVV and Route of Administration

The IVV and the routes and methods of administration should be appropriate for each type of study as described later in this document.

1.4.4. Study Design

Where studies performed by a sponsor differ from those specified in this document, the sponsor may conduct a literature search and combine these findings with the results of any preliminary experiments to justify any alternative TAS study designs. Essential parameters to be evaluated for the safety of a vaccine are local and systemic reactions to vaccination, including application site reactions and their resolution and clinical observation of the animals. The reproductive effects of the vaccine shall be evaluated where applicable.

Special tests may be required such as hematology, blood chemistry, necropsy or histological examination. Where these tests are conducted in a subset of animals, these animals should be randomly selected with adequate sampling rate before study initiation, to avoid bias, unless otherwise justified. In case of unexpected reactions or results, samples should be selected appropriately in order to identify the cause of the problem observed, if possible.

Whenever possible, the personnel collecting data in the studies should be masked (blinded) to treatment identification to minimize bias. Pathologists are not required to be masked to the type of IVV and the possible clinical effects but should be masked to the treatment groups. Histopathology data should be evaluated by recognized procedures (e.g. Crissmann et al., Toxicologic Pathology, 32 (1), 126-131, 2004).

1.4.5. Statistical Analysis

In laboratory studies the safety implications should be addressed by applying descriptive statistical methods to the data. Tables and descriptive text are common methods of data summarization; however, it may also be valuable to make use of graphical presentations in which patterns of adverse events are displayed both within treatments and within individual animals. In field studies, if applicable, selection of the general form for a statistical model and the factors to be included in the model will depend on the nature of the response variable being analyzed and the study design. Regardless of the methods chosen, the process and steps used to conduct any statistical evaluations should be described. The outcomes of the data analysis should be clearly presented to facilitate evaluation of potential safety concerns. The terminology and methods of presentation should be chosen to clarify the results and expedite interpretation.

Although there may be interest in the null hypothesis of no difference between treatments, study design constraints limit the statistical power and discriminatory ability of these studies. Under these conditions, statistical analysis alone may not detect potential adverse effects and thus provide assurance of safety. A statistically significant test does not necessarily indicate the presence of a safety concern. Similarly, a non-significant test does not necessarily indicate the absence of a safety concern. Results should therefore be evaluated based on statistical principles but interpretation should be subject to veterinary medical considerations.

2. GUIDELINES

Target animal safety for IVV is determined using laboratory and field studies. For both live and inactivated vaccines, any data collected which could be related to the safety of IVV

should be reported from studies conducted during development phase of the IVV. These data may be utilized to support TAS laboratory study design and to identify critical parameters to be examined.

Laboratory safety studies are designed to be the first step in evaluating target animal safety and are a basic requirement before initiating the field studies. The design of laboratory safety studies will vary with the type of product and intended use of the product being tested.

2.1 Laboratory Safety Tests

2.1.1 Overdose Test for Live Vaccines

For live vaccines shown to retain residual pathogenicity by induction of disease specific signs or lesions, overdose testing of the live vaccine component should be conducted as part of the risk analyses for the acceptability of the micro-organism as vaccine strain. The study should be conducted using either a pilot or production batch. A 10X dose based on the maximum release titer for which the application is submitted shall be administered. In the case where the maximum release titer to be licensed is not specified, the study should be conducted with a justifiable multiple of the minimum release titer, taking into account the need to ensure an appropriate safety margin. Exceptions need to be scientifically justified. Routinely at least 8 animals per group should be used unless otherwise justified. If adjuvant or other components are contained in a diluent for the live vaccine, the amount and concentration in a dose administered should be as proposed and justified in the draft registration dossier. If a 10X titer of antigen cannot be dissolved in 1X dose volume, then a double dose or other minimum volume of diluent sufficient to achieve dissolution should be used. The inoculum may be administered using multiple injection sites if justified by the required dose volume or the target species.

In general other vaccines do not require overdose testing.

Generally, for each target species, the most sensitive class, age and sex proposed on the label should be used. Seronegative animals should be used. In cases where seronegative animals are not reasonably available, alternatives should be justified. If multiple routes and methods of administration are specified for the product concerned, administration by all routes is recommended. If one route of administration has been shown to cause the most severe effects, this single route may be selected as the only one for use in the study. Where applicable, the titer or potency of the batches used for safety testing, particularly the overdose studies, will form the basis for establishing the maximum release titer or potency for batch release.

2.1.2 One Dose and Repeat Dose Test

For vaccines that require a single life time dose or primary vaccination series only, the primary vaccination regimen should be used. For vaccines that require a single dose or primary vaccination series followed by booster vaccination, the primary vaccination regimen plus an additional dose should be used. For convenience, the recommended intervals between administrations may be shortened to an interval of at least 14 days.

Evaluation of the one/repeat dose testing should be conducted using either a pilot or production batch of IVV containing the maximum release potency, or in the case where

maximum release potency to be licensed is not specified, then a justified multiple of the minimum release potency should be used.

Routinely at least 8 animals per group should be used unless otherwise justified. Generally, for each target species, the most sensitive class, age and sex proposed on the label should be used. Seronegative animals should be used for live vaccines. In cases where seronegative animals are not reasonably available, alternatives should be justified.

If multiple routes and methods of administration are specified for the product concerned, administration by all routes is recommended. If one route of administration has been shown to cause the most severe effects, this single route may be selected as the only one for use in the study.

2.1.3 Data Collection

General clinical observations appropriate for the type of IVV and animal species should be made every day for 14 days after each administration. In addition, other relevant criteria such as rectal temperature (for mammals) or performance measurement are recorded within this observation period with appropriate frequency. All observations should be recorded for the entire period. Injection sites should be examined daily or at other justified intervals by inspection and palpation for a minimum of 14 days after each administration of the IVV. When injection site adverse reactions are present at the end of the 14 days observation, the observation period should be extended until resolution of the lesion or, if appropriate, until the animal is euthanized and histopathological examination is performed.

2.2. Reproductive Safety Test

Examinations of reproductive performance of breeding animals must be considered when data suggest that the starting material from which the product is derived may be a risk factor. The laboratory studies in concert with the field safety studies (detailed in 2.3) are required to support use in breeding animals. If the reproductive safety studies are not performed, an exclusion statement must be included on the label, unless a scientific justification for absence of risk for use of the IVV in the breeding animal is provided. The design and extent of the laboratory and field safety studies will be based upon the type of organism(s) involved, the type of vaccine, timing and route of delivery, and the animal species involved.

For examination of reproductive safety, animals appropriate for the purpose of the study will be vaccinated with at least the recommended dose according to the vaccination scheme which is indicated. If multiple routes and methods of administration are specified for the product concerned, administration by all routes is recommended. If one route of administration has been shown to cause the most severe effects, this single route may be selected as the only one for use in the study. Routinely at least 8 animals per group should be used unless otherwise justified using either a pilot or production batch . The animals should be observed for a period appropriate to determine reproductive safety, including daily safety observations specified in 2.1.3. Exceptions should be justified. A control group should be included.

Vaccines recommended for use in pregnant animals must be tested as described above in each of the specific periods of gestation recommended for use on the label. An exclusion statement will be required for those gestation periods not tested.
The observation period must be extended, e.g. to parturition, to examine any harmful effects during gestation or on progeny. Exceptions should be justified.

When scientifically warranted, additional studies may be required to determine the effect(s) of IVV on semen including shedding of the live organism in semen. The observation period should be appropriate for the purpose of the study.

For IVVs recommended for use in future layers or laying hens, study design should include evaluation of parameters that are appropriate for the class of hens vaccinated.

2.3 Field Safety Test

Where disease and husbandry are similar between regions participating in the VICH, international data may be used for field studies, as long as a minimum proportion of the data, acceptable to the regional authorities, is generated within the region where approval is being sought. It is the responsibility of the sponsor to ensure that field studies should be conducted under animal husbandry conditions representative of those regions in which authorization is sought. Local authorizations must be obtained prior to conduct of the study. Consultation with regional regulatory authorities regarding study design prior to conduct of the studies is recommended.

If a label indicates use in breeding animals, appropriate field safety studies need to be performed to show the safety of the IVV under field conditions.

2.3.1 Animals

The animals should be in the age range/class intended for treatment as indicated in the proposed labeling. Serological status may be considered. Whenever possible either a negative or positive control group is included.
Treated and control animals are managed similarly. Housing and husbandry should be adequate for the purpose of the study and conform to local animal welfare regulations.

2.3.2 Study Sites and Treatment

Two or more different geographical sites are needed.
The recommended dosage(s) and route(s) for vaccination should be used.
The studies should be conducted using representative batch(es) of the IVV. Some regions may require that the field safety study be performed using more than one batch of product.

2.3.3 Data Collection

Observations should be made over a period of time appropriate for the IVV and adverse events should be documented and included in the final report. Reasonable attempt should be made to determine causality for the adverse event.

3. GLOSSARY

Adverse Effect: Adverse event suspected to be related to an IVV.

Adverse Event: Any observation that is unfavorable and unintended and occurs after the use of an IVV, whether or not considered to be product related.

Class: Subset of target animal species which is characterized by factors such as reproductive status and/or use (dairy vs. beef, broiler vs. layer).

Dosage: The amount of the IVV dose including volume or potency of the vaccine given (ml,), frequency and duration of administration.

Field Safety Study: Clinical study conducted by an independent investigator using the IVV under actual marketing conditions and following labeling indications to assess efficacy and/or safety.

Good Clinical Practices (GCP): A standard for the design, conduct, monitoring, recording, auditing, analysis, and reporting of 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.

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.

Investigational Veterinary Vaccine (IVV): Any live or killed vaccines being evaluated in a clinical or non-clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

Masking/Blinding: A procedure to reduce potential study bias in which designated study personnel are kept uninformed of the treatment assignment(s).

Maximum Release Potency: The expected maximum antigen content allowed at the time of release expressed in units appropriate for the IVV.

Maximum Release Titer: The expected highest number of viable organisms allowed per dose in a vaccine at the time of release, verified by safety studies.

Minimum Release Potency: The expected minimum antigen content allowed at the time of release expressed in units appropriate for the IVV.

Minimum Release Titer: The expected lowest number of viable organisms required per dose in a vaccine at the time of release, verified by efficacy and stability studies.

Negative Control: Healthy animals that are untreated or which receive a vehicle, placebo or sham treatment.

Pilot Batch: A batch of an IVV manufactured by a procedure fully representative of and simulating that to be applied at commercial scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Positive Control: Healthy animals that are given a similar vaccine, which is normally registered in the country in which the study is conducted. This product is chosen by the company (the sponsor), and it is indicated for the disease and the target species claimed for the tested IVV.

Production Batch: A batch of an IVV manufactured in the intended production facility by the method described in the application.

Protocol: A document that fully describes the objective(s), design, methodology, statistical considerations and organization of a study. The document is signed and dated by the investigator for clinical studies (or study director for GLP studies) and the sponsor. The protocol may also give the background and rationale for the study but these could be provided in other study protocol-referenced documents. The term includes all protocol amendments.

Residual pathogenicity: The potential of viruses or bacteria which have been attenuated for specific target animal species and for specific routes of administration to induce clinical signs or lesions of disease or persistence/latency of the micro-organism in the body of vaccinated animals.