CVM Guidelines and Guidance Documents

No. 85 (VICH GL9)

Good Clinical Practice

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Guidance for Industry

GOOD CLINICAL PRACTICE

No. 85 (VICH GL9)

Final Guidance

This final guidance is intended to provide guidance on the design and conduct of all clinical studies of veterinary medicinal products in the target species submitted for approval to the European Union, Japan, and the United States.

Electronic comments and suggestions regarding this document should be submitted via the Internet at: http://www.accessdata.fda.gov/scripts/oc/dockets/edocketh ome.cfm. Written comments and suggestions should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 99D-2406.

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VICH GL9 (GCP)
June 2000
For Implementation at Step 7

GOOD CLINICAL PRACTICE

Recommended for Implementation
at Step 7 of the VICH Process
on 15 June 2000
by the VICH Steering Committee

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

This guidance represents FDA's current thinking on this matter and does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternate method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

INTRODUCTION

The objective of this document is to provide guidance on the design and conduct of all clinical studies of veterinary products in the target species.

It is directed at all individuals and organizations involved in the design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species and is intended to ensure that such studies are conducted and documented in accordance with the principles of Good Clinical Practice (GCP).

Good Clinical Practice is intended to be an international scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing and reporting clinical studies evaluating veterinary products. Compliance with this standard provides public assurance about the integrity of the clinical study data, and that due regard has been given to animal welfare and protection of

the personnel involved in the study, the environment and the human and animal food chains.

This guidance has been developed under the principles of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and will provide a unified standard for the European Union (EU), Japan and the United States of America (USA) to facilitate the mutual acceptance of clinical data by the relevant regulatory authorities. This guidance was developed with consideration of the current practices in the EU, Japan and the USA together with those of Australia and New Zealand.

This guidance should be followed when developing clinical study data that are intended to be submitted to regulatory authorities.

When a guidance document states a requirement imposed by law, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guidance document.

1. GLOSSARY

1.1. Adverse Event (AE)

Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, whether or not considered to be product related.

1.2. Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) of the relevant regulatory authority addressing the conduct of studies using investigational veterinary products.

1.3. Audit

A systematic and independent examination of study related activities and documentation to determine whether the study being evaluated is or was properly conducted and whether the data are or were recorded, analyzed and accurately reported according to the study protocol, study related standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

1.4. Authenticated Copy

A copy, which is a complete reflection of an original document, that bears or contains a statement, signed and dated by the individual(s) making the copy, certifying that such copy is complete and accurate.

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

1.6. Case Report Forms/Data Capture Forms/Record Sheets
Printed, optical, electronic, or magnetic documents specifically designed to record study protocol-required and other observations of study animals or laboratory results.

1.7. Clinical Study
A single scientific experiment conducted in a target species to test at least one hypothesis relevant to the proposed effectiveness claim(s) or to in-use safety in the target animal for a veterinary product under investigation. For the purpose of this guidance, the term clinical study and study are synonymous.

1.8. Compliance (in relation to studies)
Adherence to the study protocol, relevant SOPs, Good Clinical Practice, and the applicable regulatory requirements.

1.9. Control Product
Any approved product used according to label directions, or any placebo, used as a reference in a clinical study for comparison with the investigational veterinary product

under evaluation.

1.10. Contract Research Organization (CRO)
An individual or organization contracted by the sponsor or investigator to perform one or more of the obligations of the sponsor or investigator.

1.11. Disposal of Investigational Veterinary Products
The fate of investigational veterinary and control products during or following completion of the study. For example, after complying with any restrictions to minimize public health concerns, the products may be returned to the sponsor, incinerated or disposed of by other approved methods.

1.12. Disposal of Study Animals
The fate of the study animals or their edible products during or following completion of the study. For example, after complying with any restrictions to minimize public health concerns, animals may be slaughtered, returned to the herd, sold or returned to their owner.

1.13. Final Study Report (FSR)
A comprehensive description of a study of an investigational veterinary product that is written after the collection of all raw data is complete or the study is discontinued and that completely describes the objectives and experimental materials and methods (including

statistical analyses), presents the study results and contains a critical evaluation of the study results.

1.14. Good Clinical Practice (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 the 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.

1.15. Informed Consent
A documented process by which an owner, or owner's agent, voluntarily confirms the owner's willingness to allow their animal(s) to participate in a particular study, after having been informed of all aspects of the study that are relevant to the decision to participate.

1.16. Inspection
The act by a relevant regulatory authority of conducting, in accordance with its legal authority, an official review of study documentation, facilities, equipment, finished and unfinished materials (and associated documentation), labeling, and any other resources related to the registration of an investigational veterinary product and that may be located at any site related to the study.

1.17. Investigational Veterinary Product
Any biological or pharmaceutical form of, or any animal feed containing one or more active substances being evaluated in a clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

1.18. Investigator
An individual responsible for all aspects of the conduct of a study at a study site. If a study is conducted by a group of individuals at a study site, the investigator is the leader of the group.

1.19. Monitor
An individual responsible for overseeing a clinical study and ensuring that it is conducted, recorded, and reported in accordance with the study protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

1.20. Multicenter Study
A study conducted according to a single study protocol at more than one site.

1.21. Quality Assurance (QA)
A planned and systematic process established to ensure that a study is performed and the data are collected, documented (recorded) and reported in compliance with this guidance and the applicable regulatory requirements.

1.22. Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study-related activities have been fulfilled.

1.23. Randomization
The process of assigning study animals (or groups of study animals) to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.24. Raw Data
Any original worksheets, calibration data, records, memoranda and notes of first-hand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from automated instruments, and hand-recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

1.25. Regulatory Authorities
Bodies having the statutory power to regulate. In this guidance, the expression 'regulatory authorities' includes the authorities that review submitted clinical data and conduct inspections.

1.26. Sponsor
An individual, company, institution or organization which takes responsibility for the initiation, management, and financing of a clinical study for the veterinary product under investigation.

1.27. Standard Operating Procedure (SOP)
A detailed, written instruction to facilitate consistency in the performance of a specific function.

1.28. Study Animal
Any animal that participates in a clinical study, either as a recipient of the investigational veterinary product or as a control.

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

1.30. Study Protocol Amendment
A written change or modification of the study protocol effected prior to the implementation of the protocol or execution of the changed or modified task. Study

protocol amendments should be signed and dated by the investigator and sponsor and incorporated into the study protocol.

1.31. Study Protocol Deviation
A departure from the procedures stated in the study protocol. Study protocol deviations should be recorded as a statement signed and dated by the investigator describing the deviation and the reason for its occurrence (if identifiable).

1.32. Target Animal
The specific animal by species, class and breed identified as the animal for which the investigational veterinary product is intended for use.

1.33. Veterinary Product
Any product with approved claims to having a protective, therapeutic or diagnostic effect or to affect physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

2. THE PRINCIPLES OF VICH GCP

2.1. The purpose of the VICH GCP is to establish guidance for the conduct of clinical studies that ensures the accuracy, integrity and correctness of data. Due

regard should be given to the welfare of the study animals, the effects on the environment and the study personnel, and to residues in the edible products derived from food-producing study animals.

2.2. Pre-established systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical studies are necessary to assure the validity of data and to ensure the ethical, scientific, and technical quality of studies. Data collected from studies designed, conducted, monitored, recorded, audited, analyzed and reported in accordance with this guidance can be expected to facilitate the review process, since the regulatory authorities can have confidence in the integrity of studies which follow such pre-established written procedures.

2.3. By following such pre-established written procedures, it is likely that sponsors can avoid unnecessary repetition of definitive studies. Any requirement for local effectiveness studies to confirm the findings of the definitive studies is not affected by this guidance document. In addition, other guidance may exist which define study design and effectiveness criteria for specific veterinary product categories. These studies also should be conducted according to GCP principles.

2.4. Each individual involved in conducting a clinical

study should be qualified by education, training, and expertise to perform their respective task(s). These individuals should demonstrate, in a manner that is evident from the study documentation, the highest possible degree of professionalism in the recording and reporting of study observations.

2.5. The relevant regulatory authority should provide procedures that independently assure that the study animals and the human and animal food chains are protected. The relevant regulatory authority should also assure that informed consent has been obtained from the owner of the study animals.

2.6. Studies covered by Good Laboratory Practice (GLP), basic exploratory studies or other clinical studies not intended to be used for regulatory support are not included in the scope of this guidance. However, data derived from safety and pre-clinical studies may be required to be submitted to the relevant regulatory authority in order that subsequent clinical studies may be properly authorized prior to commencement.

2.7. Wherever possible, investigational veterinary products should be prepared, handled and stored in accordance with the concepts of good manufacturing practice (GMP) of the relevant regulatory authorities. Details of preparation, handling and storage of investigational veterinary products should be documented

and the products should be used in accordance with the study protocol.

2.8. The assurance of quality of every aspect of the study is a fundamental component of sound scientific practices. The principles of GCP support the use of quality assurance (QA) procedures for clinical studies. It is perceived that the sponsor would be the party responsible for the QA functions for these studies. All participants in clinical studies are encouraged to adopt and adhere to generally recognized sound QA practices.

3. THE INVESTIGATOR

3.1. General.

3.1.1. The investigator is the individual responsible for all aspects of the conduct of the study. These would include: the dispensing and the administration of the investigational and control veterinary product(s), the implementation of the study protocol, the collection and reporting of the study data and the protection of the health and welfare of the personnel involved in the study and the animals during the study.

3.1.2. The investigator should have sufficient knowledge, scientific training and experience, as evidenced by a current curriculum vitae and other credentials, to conduct clinical studies to investigate the effectiveness and in-use

safety of investigational veterinary products in the target species. The investigator should be familiar with the background and requirements of the study before taking receipt of the investigational veterinary product.

3.1.3. If a study is conducted by a group of individuals, the investigator is the leader of the group.

3.1.4. The investigator may be assisted by trained competent staff in collecting, recording and the subsequent processing of data.

3.1.5. An individual should not serve as both the investigator and the monitor of any one study.

3.2. Responsibilities. The investigator should:

3.2.1. Submit to the sponsor, before the study is initiated, an up-to-date personal curriculum vitae and other applicable credentials.

3.2.2. Agree, by signature, to the study protocol with the sponsor that the study will be conducted according to the study protocol following the principles of GCP and applicable regulatory requirements.

3.2.3. Ensure that the study is conducted according to the study protocol, relevant SOPs, GCP and applicable regulatory requirements.

3.2.4. Maintain in the study documentation a signed and dated copy of the study protocol which includes each study protocol amendment. Each study protocol amendment, whether prepared by the sponsor or investigator, should be signed and dated by the sponsor and investigator and should identify what has been changed or modified and the reasons for such change or modification.

3.2.5. Record in a signed and dated statement, to be retained in the study documentation, any deviation from the study protocol and the reason for its occurrence (if identifiable).

3.2.6. Notify the sponsor promptly of any study protocol deviation.

3.2.7. Provide sufficient qualified personnel, including (as appropriate) a veterinarian to attend to the study animals, for the timely and proper conduct of the study. Adequately inform and provide any necessary training to personnel involved with the study or the management of the study animals to ensure compliance with the study protocol and applicable regulatory requirements.

3.2.8. Delegate any authority and work, including any subcontracted work, only to individuals qualified by training and experience to perform the assigned duties.

3.2.9. Provide relevant materials and information obtained from the sponsor to the study personnel.

3.2.10. Ensure that adequate and well-maintained facilities and equipment, whether owned or leased, are used to conduct the study.

3.2.11. Utilize Standard Operating Procedures (SOPs) for practical applications as appropriate.

3.2.12. Comply with applicable regulatory requirements governing the humane care of study animals.

3.2.13. Obtain informed consent from each owner, or owner's agent, before their animal(s) participate in the study. Each owner or owner's agent should receive relevant information regarding such participation from the investigator prior to giving their consent.

3.2.14. Supervise the housing, feeding, and care of all study animals at the study site and inform owners of animals housed off-site of their obligations as stated in the study protocol.

3.2.15. Document any veterinary care and procedures, changes in animal health, or significant environmental changes.

3.2.16. Comply with the study protocol regarding the use

of edible products derived from food-producing animals treated with an investigational and control veterinary product(s) and the proper disposal of study animals.

3.2.17. Promptly notify the sponsor of adverse events (AEs).

3.2.18. Manage any code procedure and documentation (e.g. randomization envelopes, blinding information) with professional care and ensure that any treatment code is only broken in accordance with the study protocol and with the sponsor's knowledge and consent. Study personnel who can not be or are not blinded (masked) should participate in the conduct of the study to the minimum extent necessary.

3.2.19. Be responsible for the receipt, control, storage, distribution, and further mixing with subsequent assay (if any) of the investigational and control veterinary product(s) shipped or delivered to the investigator for the conduct of the study.

3.2.20. Provide secure storage of, and control the access to the investigational and control veterinary product(s) in accordance with the study protocol and label specifications.

3.2.21. Maintain a full inventory of receipt, usage, assay results for the investigational and control veterinary

product(s) in feed or water (if further mixing by the investigator is required) and any remaining stocks of unused investigational and control veterinary product(s).

3.2.22. Ensure that the investigational and control veterinary product(s) are dispensed and administered to study animals in accordance with the study protocol.

3.2.23. Not redistribute the investigational and control veterinary product(s) to any individual not authorized to receive them.

3.2.24. At the end of the study, reconcile delivery records of the investigational and control veterinary product(s) with those of usage and returns including accounting for any discrepancies.

3.2.25. When the study is completed or discontinued, be responsible for and adequately document the safe and final disposal of the investigational and control veterinary product(s), including animal feed containing the investigational or control veterinary product(s). This may be achieved by return to the sponsor or other appropriate means of disposal.

3.2.26. Collect and retain the study documentation.

3.2.27. Document unanticipated events that may affect the quality and integrity of the study when they occur and any

corrective action taken.

3.2.28. Collect and record data, including unanticipated observations, in accordance with the study protocol and applicable regulatory requirements in an unbiased manner that accurately and completely reflects the observations of the study.

3.2.29. Prepare and maintain an accurate and complete record of all contacts including all telephone calls, visits, letters, and other contacts with representatives of the sponsor, representatives of relevant regulatory authorities and other personnel (e.g., contract research organization personnel) concerning the design, conduct, documentation, and reporting of the study. A contact record should include: the date and time of the contact; the nature of the contact; the name and organizational affiliation of all individuals involved; a summary of the purpose of the contact and subject matter discussed with sufficient detail to describe the basis of any actions that may be taken by the investigator and/or the sponsor as a result of the contact.

3.2.30. Ensure that all specimens required to be retained by the study protocol and any applicable regulatory requirements are identified in a manner that is complete, accurate, legible and precludes loss of identification from the specimen.

3.2.31. Securely store, protected from deterioration, destruction, tampering, or vandalism, all study documentation or authenticated copies of study documentation required to be retained by the investigator for the period of time required by the relevant regulatory authorities.

3.2.32. Provide to the sponsor on request either the signed study documentation or an authenticated copy. When all or part of the study documentation is forwarded to the sponsor, an authenticated copy of the forwarded information should be retained by the investigator.

3.2.33. Participate, when applicable, in the preparation of the final study report.

3.2.34. Permit monitoring and quality auditing of a clinical study.

3.2.35. Permit the relevant regulatory authority to inspect the facilities used by the investigator for the study and to inspect and copy any or all of the study documentation made or kept by the investigator as part of or pertaining to the study for the purpose of verifying the validity of the data.

4. THE SPONSOR

4.1. General. An individual, company, institution or

organization which takes responsibility for the initiation, management, and financing of a clinical study for the veterinary product under investigation.

4.2. Responsibilities. The sponsor should:

4.2.1. Ascertain that sufficient scientifically valid information exists with respect to the effectiveness and safety of the investigational veterinary product to justify conduct of the clinical study. The sponsor should also determine from this information that there are no environmental, animal welfare, or scientific grounds which might preclude the conduct of a clinical study.

4.2.2. Ensure that notification or application relating to the conduct of the study has been submitted to the regulatory authorities where required.

4.2.3. Select the investigator(s) and assure their qualifications, determine their availability for the entire duration of the study, confirm that they agree to undertake the study in accordance with an agreed study protocol, GCP and applicable regulatory requirements.

4.2.4. Appoint appropriately qualified and trained monitor(s).

4.2.5. Arrange, as necessary, for the preparation of SOPs for the procedural and technical elements of the study.

4.2.6. Prepare a study protocol, in consultation with the investigator as appropriate, giving due regard to the above considerations and consistent with the principles for GCP.

4.2.7. Sign, along with the investigator, the study protocol as an agreement that the clinical study will be conducted according to the study protocol. Any amendments to the study protocol should have the signed agreement of both sponsor and investigator.

4.2.8. Ensure, for multicenter studies, that:

4.2.8.1. All investigators conduct the study in strict compliance with the study protocol agreed to by the sponsor and if required, by the regulatory authority.

4.2.8.2. The data capture system is designed to capture the required data at all multicenter study sites. For those investigators who are collecting additional data requested by the sponsor, supplemental data capture systems should be provided and designed to capture the additional data.

4.2.8.3. All investigators are given uniform instructions on following the study protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings and on capturing data.

4.2.8.4. Communication between investigators is facilitated.

4.2.9. Inform the investigator of appropriate chemical, pharmaceutical, toxicological, safety, effectiveness and other relevant information as a prerequisite to conducting the study. The sponsor should also inform the investigator of any such pertinent information that becomes available during the study and when required, ensure that the relevant regulatory authority is also notified.

4.2.10. Report all AEs in accordance with applicable regulatory requirements.

4.2.11. Ensure the proper disposal of all study animals and any edible products derived from them according to the applicable regulatory requirements.

4.2.12. Ensure that the investigational and control veterinary product(s) have been prepared, labeled and shipped according to requirements of the relevant regulatory authority.

4.2.13. Prepare and retain records of shipment of the investigational veterinary and control product(s). When the study is completed or discontinued, ensure the proper and final disposal of all supplies of the investigational and control veterinary product(s) and any animal feed containing the investigational or control veterinary product.

4.2.14. Maintain study documentation, protected from deterioration, destruction, tampering or vandalism, for as long as required to fulfill applicable regulatory requirements in the countries where the study has been submitted in support of the registration of the investigational veterinary product.

4.2.15. In the event that an animal is treated with an investigational veterinary product, arrange for a study report to be written whether or not the study has been completed as planned.

4.2.16. Ensure the quality and integrity of data from clinical studies by implementing quality audit procedures that are consistent with well-recognized and accepted principles of quality assurance.

4.2.17. Comply with the applicable regulatory requirements governing the humane care of study animals.

4.3. Delegations to a CRO.

4.3.1. A sponsor may delegate any or all of the sponsor's study-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the study data always resides with the sponsor.

4.3.2. Any study-related duty or function that is delegated to a CRO should be specified in writing. The sponsor

should notify the CRO of its responsibility to comply with applicable regulatory requirements.

4.3.3. Any study-related duties or functions not specifically delegated to a CRO are retained by the sponsor.

4.3.4. All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the study-related duties and functions of a sponsor.

5. THE MONITOR

5.1. General. An individual appointed by the sponsor to be responsible to the sponsor for monitoring and reporting on progress of the study, verifying the data and confirming that the clinical study is conducted, recorded and reported in compliance with GCP and applicable regulatory requirements. The monitor should have scientific training and experience to knowledgeably oversee a particular study. The monitor should be trained in quality control techniques and data verification procedures. The monitor should understand all applicable protocol requirements and be able to determine whether the study was conducted in accordance with the protocol and relevant SOPs. An individual should not serve as both the monitor and investigator for any one study. The monitor is the principal communication link between the sponsor and the investigator.

5.2. Responsibilities. The monitor should:

5.2.1. Assist the sponsor to select the investigator when requested.

5.2.2. Be reasonably available to the investigator for consultation in person, by telephone or by other means.

5.2.3. Determine that the investigator and staff have sufficient time to devote to the study. Also, determine that the study site has adequate space, facilities, equipment and staff and that an adequate number of study animals is likely to be available for the duration of the study.

5.2.4. Confirm that the study staff has been adequately informed about the details of the study.

5.2.5. Ensure that the investigator accepts responsibility for conducting the study and in so doing understands: the investigational status of the veterinary product under evaluation; the nature and details of the study protocol; the applicable regulatory requirements governing the humane care of study animals; the conditions of any authorization for the use of edible products derived from food-producing animals treated with the investigational or control veterinary product(s) and any other applicable restrictions on the disposal or subsequent use of study animals.

5.2.6. Work according to the sponsor's requirements, visit the investigator with sufficient frequency before, during and after the study to control adherence to the study protocol, GCP and applicable regulatory requirements.

5.2.7. Not, in any way, bias the data collection process or outcome of the study, other than to ensure that the current study protocol, relevant SOPs, GCP, and applicable regulatory requirements are being followed.

5.2.8. Ensure that informed consent is obtained and recorded from the owner(s) or owner's agents prior to their animals participating in the study.

5.2.9. Ensure that all data are correctly and completely recorded.

5.2.10. Ensure that illegible, missing or corrected study documentation is fully explained.

5.2.11. Confirm that the storage, dispensing and documentation of the supply of the investigational and control veterinary product(s) are safe and appropriate and ensure that any unused products are returned by the investigator to the sponsor or disposed of properly.

5.2.12. Review the raw data and other study documentation necessary to determine that the study

protocol is being followed and the information maintained or kept by the investigator is accurate and complete.

5.2.13. Prepare and maintain an accurate and complete record of all contacts including all telephone calls, visits, letters and other contacts with the investigator, representatives of the sponsor, representatives of relevant regulatory authorities and other personnel (e.g., contract research organization personnel) concerning the design, conduct, documentation, and reporting of the study. A contact record should include: the date and time of the contact; the nature of the contact; the name, and organizational affiliation of all individuals involved; a summary of the purpose of the contact and subject matter discussed with sufficient detail to describe the basis of any actions that may be taken by the investigator and/or the sponsor as a result of the contact.

5.2.14. Confirm investigator compliance to the principles of GCP by providing a signed and dated summary report of the contacts, visits made and activities witnessed during the conduct of the study. This summary report should be submitted to the sponsor at the end of the study.

6. THE STUDY PROTOCOL

6.1. General.

6.1.1. A study protocol is a document that states the

objectives of the study and defines the conditions under which the study is to be performed and managed.

6.1.2. A well-designed study relies predominantly on a thoroughly considered, well-structured and comprehensive protocol which should be completed and approved by the sponsor and investigator before the study is initiated.

6.1.3. A comprehensive study protocol that is easily understood by the investigator executing the study and by the relevant regulatory authority reviewing the protocol and study results may facilitate the registration process for veterinary products.

6.2. Study Protocol Review. Review of the study protocol by the relevant regulatory authority prior to the initiation of the clinical study is encouraged within the principles of GCP particularly when there is any uncertainty about a proposed study design or there are differing opinions about the relevance of several options for conducting the study. Review of the study protocol by the relevant regulatory authority does not bind the authority to accept the data collected from a study conducted using such a study protocol. However, it is expected that both the sponsor and the relevant regulatory authority would benefit from such a review, in terms of a mutual understanding of the regulatory requirements and the relevance of the objective(s) of the study protocol.

6.3. Study Protocol Check List. The study protocol should contain the information given in the following list of items or this list should be considered whenever a study is contemplated. The list provided is not exhaustive nor is every item included applicable to all study protocols but it is intended to give guidance:

6.3.1. Title of the study.

6.3.2. Identifier unique to the study. A unique identifier consists of a study protocol number, the status of the study protocol (i.e., draft, final, amended) and the date of the version of the study protocol, all of which should be clearly located on the title page.

6.3.3. Study contacts. Study contacts include the investigator, representatives of the sponsor and all other participants responsible for major aspects of the study. List, for each contact, the title, qualifications, professional background, as well as the postal address telephone number and other communication means.

6.3.4. Identity of the sites (if known at the time of study protocol preparation).

6.3.5. Objective(s)/purpose of the study.

6.3.6. Justification. Describe all information where relevant to the understanding of the objective of the study

(pre-clinical or clinical data published or otherwise available) that justifies the conduct of the clinical study.

6.3.7. Schedule of events. Schedule of key events occurring during the animal phase of the study including: the expected date and time of commencement of the animal phase, the period during which the investigational and control veterinary product(s) are being administered, the post administration observation period, the withholding period (when applicable) and the termination date where known.

6.3.8. Study design. Describe:

6.3.8.1. The overall design of the study, e.g. a placebo control clinical field effectiveness study or a randomized blocked design versus a positive control, with blinding.

6.3.8.2. The treatment, if any, in detail to be applied to control group(s) or for control period(s).

6.3.8.3. The randomization method, including the procedures to be adopted and practical arrangements to be followed to allocate animals to treatment groups and treatment groups to experimental units.

6.3.8.4. The experimental unit(s) and justify their selection.

6.3.8.5. The extent and methods of blinding (masking) and other bias reducing techniques to be used and state the provisions, including procedures and personnel, for access to treatment codes.

6.3.9. Animal selection and identification. Specification of the source, number, identity and type of study animal to be used, such as species, age, gender, breed category, weight, physiological status and prognostic factors.

6.3.10. Inclusion/exclusion and post-inclusion removal criteria. Specify objective criteria for the exclusion from, inclusion in and removal subsequent to inclusion in the study.

6.3.11. Animal management and housing. Describe:

6.3.11.1. The containment of the study animals, e.g. pens, kennels, pastures.

6.3.11.2. Space allocation per animal (in comparison to standard management practices).

6.3.11.3. The thermoregulation (heating/cooling) and ventilation of animal accommodation.

6.3.11.4. Permissible and non-permissible concomitant veterinary care and therapy.

6.3.11.5. The management of feed (including pasture management and the preparation and storage of mixed feeds) and water (including supply, availability and quality) and their presentation to the study animals.

6.3.12. Animal feeds. Authoritative reference sources may serve as useful guides in the determination of the nutritional requirements of the study animals and preparation of feeds. The ration-related study documentation should be sufficient to establish that the nutritional requirements of the animals are met so as not to compromise the objectives of the study and to ensure that animal welfare requirements are met. Where nutritional status can be critical to the measurements to be collected in the study, detailed records of feed characteristics should be collected. As appropriate:

6.3.12.1. Determine the nutrient needs of the study animals and prepare feeds meeting these needs.

6.3.12.2. Provide quantitative composition (e.g., feedstuffs, vitamins, minerals and, as appropriate, permissible feed additives) and calculated nutrient densities for all feeds used in the study.

6.3.12.3. Describe procedures for the sampling of the feed used in the study and subsequent analysis of these samples for selected nutrients.

6.3.12.4. Develop and follow objective criteria to determine whether feeds used in the study, based on actual laboratory nutrient analyses, meet the pre-determined calculated requirements.

6.3.12.5. Provide a feeding program (feeding schedule).

6.3.12.6. Collect records of the amount of feed offered and refused.

6.3.13. Investigational veterinary and control product(s).

6.3.13.1. Clearly and precisely identify the investigational veterinary product to readily permit an unambiguous determination of the specific formulation. Instructions for the further mixing (if any), packaging and storage of these products should be stated.

6.3.13.2. If the investigational veterinary product is administered in feed or water, describe the procedures for determining the concentration of the investigational veterinary product in the feed or water, including the sampling methods and assay methodologies (e.g. laboratory used, analytical method, number of replicates, assay limits, permitted analytical variation) to be used. Develop and follow objective criteria to determine whether the investigational veterinary product concentration in the feed or water is adequate.

6.3.13.3. Identify control products by generic or trade name; dosage form, formulation (ingredients); concentration; batch number; expiry date. Store and use these products according to label directions.

6.3.14. Treatments. For the investigational and control veterinary product(s):

6.3.14.1. Justify the dosing to be used.

6.3.14.2. Describe the dosing regimen (route, site of injection, dose, frequency and duration of administration) to be followed in administering the products.

6.3.14.3. Specify objective criteria for the potential use of concomitant veterinary treatment.

6.3.14.4. Describe the methods and precautions to be taken to ensure the safety of study personnel handling these products prior to and during administration.

6.3.14.5. Describe measures to ensure administration of these products in compliance with the study protocol or its labeling.

6.3.15. Disposal of study animals, products of study animals and investigational and control veterinary product(s).

6.3.15.1. Describe the proposed disposal of the study animals.

6.3.15.2. Describe the care to be given to animals removed from the study in accordance with pre-established criteria.

6.3.15.3. State the conditions for use of edible products from food-producing animals that must be followed in order to comply with the authorization granted by the relevant regulatory authority.

6.3.15.4. Describe the proposed disposal of the investigational and control veterinary product(s).

6.3.16. Assessment of effectiveness.

6.3.16.1. Define the effects to be achieved and the clinical end-point(s) to be reached before effectiveness can be claimed.

6.3.16.2. Describe how such effects and end-points are to be measured and recorded.

6.3.16.3. Specify the timing and frequency of study observations.

6.3.16.4. Describe the special analyses and/or tests to be performed, including the time of sampling and the interval

between sampling, storage of samples, and the analysis or testing.

6.3.16.5. Select and define any scoring system and measurements that are necessary to objectively measure the targeted response(s) of the study animal and evaluate the clinical response.

6.3.16.6. Define the methods for computing and calculating the effect of the investigational veterinary product.

6.3.17. Statistics/Biometrics. Thoroughly describe the statistical methodologies to be used to evaluate the effectiveness of the investigational veterinary product, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made, and the level of significance, the experimental unit and the statistical model to be used. The planned sample size should be justified in terms of the target animal population, the power of the study and pertinent clinical considerations.

6.3.18. Handling of records. Specify procedures for recording, processing, handling, and retaining raw data and other study documentation required by the relevant regulatory authority.

6.3.19. Adverse events. Describe procedures for:

6.3.19.1. Observing study animals with sufficient frequency to detect AEs.

6.3.19.2. Taking appropriate actions in response to observed AEs. Appropriate actions may involve, among other items, locating and breaking blinding codes so that appropriate medical treatment can be given.

6.3.19.3. Recording of the AEs in the study documentation.

6.3.19.4. Reporting AEs to the sponsor.

6.3.20. Supplements to be appended to the protocol.

6.3.20.1. List any study-specific SOPs that apply to the conduct, monitoring and reporting of the study.

6.3.20.2. Attach a copy of all data capture and event record forms to be used during the study.

6.3.20.3. Include any other relevant supplements, e.g. information to be provided to the owners of animals, instructions to study personnel.

6.3.21. Changes to the study protocol. Instructions for preparation of amendments and reporting of deviations to the study protocol should be provided.

6.3.22. References. Provide citations to relevant literature referenced in the study protocol.

7. THE FINAL STUDY REPORT

7.1. General.

7.1.1. The final study report (FSR) is a complete and comprehensive description of the study written after its completion. It includes a description of the materials and methods, a presentation and evaluation of the results, statistical analyses and a critical clinical, scientific and statistical appraisal. The report should follow the format of the study protocol.

7.1.2. The sponsor should provide a FSR for any study in which an animal has been treated with an investigational veterinary product whether or not the study has been completed as planned.

7.2. Authorship.

7.2.1. The preparation of this report can be accomplished as follows:

7.2.1.1. The sponsor may prepare the FSR;

7.2.1.2. The investigator may prepare the FSR for the sponsor; or

7.2.1.3. The sponsor and investigator may prepare the FSR through a collaborative effort.

7.2.2. All individuals involved in the preparation of the FSR would be considered author(s).

7.2.3. When an investigator relinquishes authorship of the FSR, the investigator should provide to the authors:

7.2.3.1. All necessary study documentation specific to the site at which the investigator conducted the study, and

7.2.3.2. A signed and dated document, to be included in the FSR, which adequately describes the study documentation provided to the author(s) and attests to the accuracy and completeness of the documentation provided.

7.2.4. The authors of the FSR should sign and date the report. Authors of the FSR should be aware that the regulatory authorities view these signatures as an affirmation that all data were collected in compliance with the study protocol, relevant SOPs, GCP and applicable regulatory requirements, and that all statements are accurate and complete representations of study activities and results and are fully supported by the study documentation. Therefore, the authors may wish to include in the report a brief statement describing their contributions to the report.

7.3. Content of Final Study Report. The FSR should include relevant information from the following list. The list provided is not exhaustive nor is every item included applicable to all FSRs, but it is intended to give guidance. The study protocol section should be consulted for an explanation of the items in this list.

7.3.1. Title and identifier of the study.

7.3.2. Objectives of the study.

7.3.3. The titles, names, qualifications and roles of all people involved in conducting key elements of the study.

7.3.4. The identity of the site(s) at which the study was conducted.

7.3.5. Key study dates.

7.3.6. Materials and methods.

7.3.6.1. Study design.

7.3.6.2. Animal selection and identification.

7.3.6.2.1. Full details of study animals in each group, including but not limited to: numbers, breed, age, gender and physiological status.

7.3.6.2.2. Disease history of the animals, where available and if appropriate, relevant to the condition under investigation, especially in the case of specific disease problems associated with an animal unit.

7.3.6.2.3. Where appropriate, diagnosis of the condition being treated or prevented, including a description of the clinical signs or other diagnostic methods according to conventional criteria.

7.3.6.2.4. Detailed inclusion and exclusion criteria applied to the selection of study animals.

7.3.6.2.5. Full information on any study animal removed subsequent to inclusion in the study.

7.3.6.3. Animal management and housing.

7.3.6.3.1. Details of animal housing and management.

7.3.6.3.2. Composition of feed and the nature and quantity of any additives in the feed.

7.3.6.3.3. Details of any concomitant treatment administered during the study, either prior to, during or after treatment with the investigational veterinary or control product(s), and details of any interactions observed.

7.3.6.4. Animal disposal. A summary of the disposal of the study animals and their edible products.

7.3.6.5. Treatments.

7.3.6.5.1. The identification of the study investigational formulation used in the study, including strength, purity, composition, quantity, and batch or code mark.

7.3.6.5.2. The dosage of the investigational veterinary product, method, route and frequency of administration, and precautions, if any, taken during administration.

7.3.6.5.3. Details of the control product(s) used with a justification for their selection.

7.3.6.5.4. The duration of treatment and observation periods.

7.3.6.5.5. A summary of use and disposal of all investigational veterinary product and control product(s) shipped or delivered to the investigator.

7.3.6.6. Study procedures. A full description of the methods used including, if applicable, assay methods used to determine investigational veterinary product concentration in feed, water, body fluids and tissues.

7.3.6.7. Statistical methods. A description of the

transformations, calculations or operations performed on the raw data and any statistical methods employed to analyze the raw data. Reasons should be given if the statistical methods used differed from those proposed in the study protocol.

7.3.7. Results and their evaluation. A full description of the results of the study, whether favorable or unfavorable, including tables of all data recorded during the study.

7.3.8. Conclusions based on each individual case or treatment group as appropriate.

7.3.9. Administrative and compliance items.

7.3.9.1. A description of the procedures used to record, process, handle and retain raw data and other study documentation.

7.3.9.2. A description of any protocol deviations and/or amendments, and an assessment of their impact on the outcome of the study.

7.3.9.3. A description of circumstances that could have affected the quality or integrity of the data, specifying the time frame and the extent of their occurrence.

7.3.9.4. Details of any AEs occurring during the study and any measures taken in consequence. For all studies where

no AE was observed or recorded, a statement to this effect should be included in the FSR.

7.3.9.5. The location of all study documentation.

7.3.10. Additional information. Additional information such as the following may be included in the body of the report or as an appendix:

7.3.10.1. Study protocol

7.3.10.2. Dates of monitoring visits

7.3.10.3. Audit certification by auditor, consisting of the dates of site visits, audits and when reports were provided to the sponsor.

7.3.10.4. Supplementary reports, e.g. analytical, statistical, etc.

7.3.10.5. Copies of study documentation supporting study conclusions

7.4. Report Amendments. Any addition, deletion, or correction to the FSR should be in the form of an amendment by the authors. The amendment should clearly identify that part of the FSR that is being added, deleted or corrected and the reasons for the change(s), and should be signed and dated by the authors. Minor errors,

e.g., typographical errors, noted after finalization of the report may be indicated directly on the FSR when accompanied by the signature or initials of the authors, the date of the change and the reason for the change.

8. STUDY DOCUMENTATION

8.1. General.

8.1.1. Study documentation consists of those records that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced. Filing study documentation, or authenticated copies thereof, at the investigator and sponsor sites in a timely manner can greatly assist in the successful management of a study by the investigator and sponsor.

8.1.2. All study documentation should be retained for the period of time required by relevant regulatory authorities. Any or all of the study documentation described in this guidance is subject to, and should be available for, monitoring on behalf of the sponsor. Study documentation should be audited by the sponsor's quality audit procedures, consistent with well-recognized and accepted principles of quality assurance. When a quality audit is conducted, the auditor should prepare a report for the sponsor which details the auditing process and which certifies that the audit has been conducted.

8.1.3. Any or all of the study documentation described in this guidance may be inspected, audited and copied by the relevant regulatory authority as part of the process to confirm the validity of the study conduct and the integrity of the data collected.

8.1.4. The requirements for the submission of study documentation should be governed by the relevant regulatory authority.

8.2. Categories of study documentation. Study documentation should include, but is not limited to:

8.2.1. Study protocol. This documentation consists of the original study protocol, all protocol amendments and records of all protocol deviations.

8.2.2. Raw data. The raw data of a study generally includes several classes of data. Neither the classes below nor the examples provided for each class are intended to be all-inclusive.

8.2.2.1. Animal records. All pertinent data relating to the study animals, such as: purchase records, documentation of animal exclusion from, inclusion in and removal subsequent to inclusion in the study, informed consent of the owner, treatment assignment, all recorded observations (including analytical assay results of biological samples), case report forms, adverse events,

animal health observations, composition and nutrient assay of animal feeds and final animal disposal.

8.2.2.2. Investigational and control veterinary product records. All pertinent records of the ordering, receipt, inventory, assay, use or administration (documenting the dosing regimen, e.g. dose, rate, route, and duration of administration), return, and/or disposal of all the investigational and control veterinary product(s) including any animal feed containing the investigational or control veterinary product.

8.2.2.3. Contact records. The monitor's and investigator's records of all contacts (e.g. visits, telephone, written and electronic) relating to the design, conduct, documentation, and reporting of a study.

8.2.2.4. Facility and equipment records. As appropriate, descriptions of the study site, e.g. diagrams and photographs, equipment identification and specifications, equipment calibration and maintenance records, equipment failure and repair records, meteorological records and environmental observations.

8.2.3. Reports. Reports consist of:

8.2.3.1. Safety reports. Reports of adverse events.

8.2.3.2. Final study report.

8.2.3.3. Other reports. For example, statistical, analytical, and laboratory reports.

8.2.4. Standard operating procedures and reference materials. These include any reference materials and SOPs related to key elements of the study.

8.3. Recording and handling study documentation.

8.3.1. Raw data, whether handwritten or electronic, should be attributable, original, accurate, contemporaneous and legible. Attributable means the raw data can be traced by signature (or initials) and date to the individual who observed and recorded the data. If more than one individual observes or records the raw data, that fact should be reflected in the data entries. In automated data collection systems, the individual(s) responsible for direct data input should record their name along with the date at the time of data input. Original and accurate means the raw data are the firsthand observations. Contemporaneous means the raw data are recorded at the time of observation. Legible means the raw data are readable and recorded in a permanent medium, e.g. ink for written records or electronic records that are unalterable.

8.3.2. Raw data should be maintained in an organized manner and, where appropriate, should be recorded in a bound laboratory notebook or on pre-established forms

designed specifically for recording particular observation(s). Records should be diligently completed with all data points recorded as required in the study protocol. When additional observations are warranted, e.g. to provide additional information for pre-planned observations or observation of unanticipated events, such observations should also be recorded.

8.3.3. Units used to measure observations should always be stated and transformation of units should always be indicated and documented. Values of laboratory analyses should always be recorded on a record sheet or attached to it. If available, normal reference values for the laboratory analyzing the specimens should be included.

8.3.4. If a portion of the raw data needs to be copied or transcribed for legibility, an authenticated copy of that data should be made. The reason for the copying or transcription should be explained in a dated memorandum or in a dated notation on the transcribed record, signed by the individual(s) making the copy or transcription. In such a case the copied raw data, the copy or transcript of the raw data and the memorandum should be kept together in the study documentation.

8.3.5. Any correction in the hand-written study documentation should be made by drawing one straight line through the original entry. The original entry should still be legible. The correction should be initialed and

dated by the individual(s) making the correction at the time the correction is made and should describe the reason for the change.

8.3.6. Similarly, if data are entered directly into a computer system, the electronic record is considered the raw data. A computerized system should ensure that the methods for record keeping and retention afford at least the same degree of confidence as that provided with paper systems. For example, each entry, including any change, should be made under the electronic signature of the individual making the entry, and any changes that are made to data stored on electronic media should be maintained in an audit trail to protect the authenticity and integrity of the electronic records.

8.4. Retention of study documentation.

8.4.1. All study documentation should be stored in a manner that protects it from deterioration, destruction, tampering or vandalism in accordance with the nature of the records. The storage site should permit the orderly storage and easy retrieval of the retained documentation.

8.4.2. The location of the study documentation, and any authenticated copy, for a study should be specified in the final study report.

8.4.3. All study documentation should be retained for an

appropriate period of time to satisfy the requirements of the relevant regulatory authorities to which the study may be or has been submitted in support of the registration of the investigational veterinary product.

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