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Susanne Zänker

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This book is dedicated to

Harefield Transplant Hospital
(Middlesex)

and

Queensview Medical Center
(Northampton)
Foreword

Susanne Zänker

A genius is a talented person who does his homework.
Thomas A. Edison, 1847–1931

The concept of Good Clinical Practice (GCP) has its source in the United States and is intended to give guidance on the best practice for running clinical trials in humans. The importance of this concept was acknowledged rapidly in other regions of the world, and consequently rules had been set for carrying out controlled studies to establish the safety and efficacy of new veterinary medicinal products to support an application for a marketing authorization. In view of the current stream of harmonization of standards and the globalization of business, the need to also have globally acceptable standards for veterinary medicinal products was expressed by both regulatory authorities and industry.

For that purpose, in 1996, under the initiative of the Office International des Epizooties (OIE), the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was created. In the VICH process, industry and authorities are collaborating to develop harmonized regulatory requirements based on science that will also lead to a reduction of animals needed for tests, as studies will be mutually recognized. One of the first topics identified for harmonization was GCP. The approval of this VICH guideline by all three of the regions involved, namely, the European Union, the United States and Japan, on 15 June 2000 (for implementation by July 2001) was a major milestone in the history of both international harmonization of standards and the concept of GCP. This book aims to explain this concept and to give guidance about the role and responsibilities of all those who are involved in the design and realization of clinical trials, including
clinical investigators, monitors, veterinary surgeons and nurses, sponsors and auditors.

In clinical trials, the efficacy and safety of a veterinary medicinal product are tested under more or less real conditions. In fact, as clinical trials are the last step in a long research and development process, by this stage much time and expenditure have already been invested in the future product.

It is therefore of paramount importance to have a clear understanding of what is required in a clinical trial in order to ensure the smooth progress of the project toward the next and final step—the registration of the product. It should be kept in mind that the duration of the development programme of a medicinal product, from its chemical conception until the marketing authorization, typically is between 8 and 10 years, and the costs involved amount to many millions of Euros. The veterinary medicinal market is relatively small and highly fragmented; therefore, the return on investment for each product is very limited when compared to human medicinal products, even though the investments in development are similar.

This comprehensive book provides some scientific, biological and regulatory background, which will be invaluable to teachers, research workers, regulatory affairs staff and those directly involved in clinical trials. It also provides specific guidance for each animal species, taking into account the differences and needs in the management system.

Indeed, multidisciplinary knowledge is needed to design and carry out clinical trials, as different conditions have to be respected for fish, poultry, companion animals, calves, sheep, equidae and so on. The roles and responsibilities of investigators, sponsors and monitors need to be clearly defined. Above all, success is possible only if the study is carefully designed, the personnel are qualified and committed and, equally important, continuous communication among all involved people is ensured.

More procedural aspects, such as quality assurance, Standard Operating Procedures for designing and reporting, statistical analysis and auditing, complement the practical aspects, thereby helping to make this book a valuable reference.

The reader will quickly realize that this book is a unique achievement, which was possible only through the hard work, team spirit and co-operation of all the authors involved.

It was my personal pleasure to read all of the chapters, and a great honor to write a foreword to this book. It acknowledges FEDESA's contribution to the improved understanding and implementation of GCP in Europe in 1993/94 and thereafter at an international level through its involvement in VICH.

Susanne Zänker
FEDESA
Brussels, Belgium
December 2000
Publication of this book would not have been possible without the help and enthusiastic support of Susanne Zänker and Sophie Federicks (FEDESA). Thanks also to Tracey Kiford and Jane Steinmann of Interpharm for their patience, understanding and guidance in the preparation of this book.

We finally would like to acknowledge the help given by Ramzan Visanji's family, Koy Kee, Kassam and Yasmin Visanji, from concept to completion of the book. We are greatly indebted to them for their significant contribution.

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Introduction and Overview of Setting Up Studies to Good Clinical Practice

Nigel Dent

As one of the co-editors of this book, I thought it would be useful for the first chapter to not only introduce the authors and their chapters but give the reader an overview of the objectives that the book sets out to achieve. This chapter also summarises the rather complex picture of setting up clinical trials in the ever-changing environmental and regulatory field of veterinary clinical trials.

One of the key problems that all companies face in times of mergers, acquisitions or collaborative agreements, which seem to be buzz words in the industry at the moment, are a lack of resources, decreased time lines and an ever-shrinking market. It is strange that over the past years, terminology, such as the ambiguous Gulf War American phrase, “killed by friendly fire”, usually heralds disaster. Whatever the term is, it usually means that one party in the merger will experience downsizing and an increase in workload for the remaining people. We also have the ever-changing regulatory attitudes and the fact that there is still no clear delineation in many areas between the need to carry out a study according to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP).
Although companies are frequently requested to consult with their local regulatory group, at the end of the day, the regulators do not always come up with a definite answer. It is ultimately the sponsor who has to make the decision on whether or not a study should be conducted according to the appropriate good practice and in turn hope that the initial decision bears fruit.

**EVALUATION OF GOOD PRACTICES**

From the point of view of GLP, this has become a standard set of tests which, in the animal health industry, has been quite transparent and easily implemented by all companies since the late 1970s. Turning, however, to the European Code of Conduct for GCP, it is being superseded by the Veterinary International Conference on Harmonisation (VICH) guidelines, a new and all embracing set of guidelines.

The problem for the animal health industry is similar to that currently faced by the human clinical trials industry, where we have a series of guidelines which enable the establishment of a good clinical study. In the animal health industry, there is not a directive to enforce appropriate guidelines or, for that matter, an inspectorate to examine the companies who are conducting clinical trials. Thus, it is generally up to the sponsor company to make a claim of GCP compliance.

It is hoped that early in the 21st century not only will the VICH document become the internationally accepted standard for conducting veterinary clinical trials according to GCP but also that a directive, certainly in the European Union (EU), will enhance the guideline and establish an inspectorate to ensure that the claim of compliance made by sponsors is backed up by a regulatory inspection.

**BACKGROUND TO THE AUTHORS AND THE CHAPTERS**

In putting together this volume, the co-editors have identified a need in the veterinary industry for this book. There are many people setting up clinical trials to varying standards and involving different species that pose different problems. Although there is a wealth of experience in the industry, this tends to be retained within companies and is not readily available as an off-the-shelf textbook.

All of the authors in this book have been approached for their knowledge and long-standing expertise of in their own particular area. The chapters themselves have been organised as a practical guide, and a large amount of the documentation is based on the authors' personal experiences, both pitfalls and benefits. Hopefully, the chapters will act as a guide to both the novice, giving areas to avoid, and to the established practitioner offering alternative ways of conducting studies but especially to ensure that these studies will meet the compliance required.
OBJECTIVE OF STUDIES

As you will see from the table of contents, we have tried to address the setting up of clinical studies in all of the major species where regulatory requirements insist that studies be conducted to GCP. Where "grey areas" arise, one can usually make a calculated guess as to whether these should be GCP or GLP studies.

Irrespective of the final good practice route chosen, I would suggest that any good practice is merely common sense, good science, and the use of qualified facilities along with good equipment. If these basic concepts are followed, then the good practice will automatically fall into place.

The general concept of conducting a study according to a good practice will never in any situation overcome the need for good science, a good study design and a careful and well-thought-out study plan. In my experience as a scientific consultant, I have seen a large amount of work conducted to the highest compliance of GCP, but the scientific integrity of the data is almost zero.

CONTROL OF STUDIES

We are all very keen to ensure that a study is conducted according to a good practice and that there is an independent review of that study by the quality assurance unit (QAU). The monitor is responsible for ensuring that the data are accurate and reflect both the study plan and the operating procedures that govern that study. In fact, all of these chapters will readily lead you to the fact that there is a need to conduct a study to a standard, which is GCP.

I would, however, suggest that one of the main considerations, prior to even reviewing whether or not the study plan complies with GCP, is to implement a very thorough and stringent quality control (QC) checking system at every available opportunity. A good QC system will include checking that the study plan meets the scientific objective and that the case report book is logical and assists the investigator in recording the site data. In addition, the staff and equipment are well trained and well maintained, respectively. Education in data recording to make sure that each entry is correct, calculations checked and the data subjected to a high level of quality control will go a long way to ensure that these data automatically comply with good practice. Anyone performing a QC check should take into account three essential questions:

1. What was done?
2. Who did it?
3. When was it done?

In other words, a clear description of the activity with a confirmatory signature and a date goes a long way to ensure that the data automatically become accepted for GCP.
Turning to the final report, we must bear in mind who the reader is. The reader of the document in most cases is a regulator sitting in isolation from the clinical study. Therefore, the report itself must be clear, concise, unambiguous and, above all, very accurate. This person's sole aim in life is to read as many documents as possible to get as many products to the market. If, in the first few pages, there are indications that the report shows poor quality or that little QC has been carried out, then the report itself will suffer from being put to the bottom of the pile to be dealt with later. Of all systems, the QC checking of the final report is of paramount importance.

**REGULATION VERSUS COMPLIANCE**

We must be very careful that we understand the two concepts described here—regulation and compliance. Regulation is governed by the Regulatory Affairs Department of a company and is reviewed by the local Veterinary Medicines Directorate (VMD). Here, we are looking to ensure that an Animal Test Certificate (ATC) is in place and that the study is allowed to progress. Similar but often different systems will be in place in different countries. The regulatory reviewer will look to see if the product is effective and safe and that there are sufficient data available to support the claim made by the sponsor to allow the reviewer to make an evaluation to give the product a licence or a marketing application.

Compliance, on the other hand, is merely a review by an independent body, such as a regulatory inspectorate, who may or may not be from the same regulatory department. Their aim in life is to ensure that the aspects of safety, animal welfare, insurance and ethics are all considered and that the GCP guidelines have been followed. Their prime concern is to see that the QC system has been put into place and that on every possible occasion QC checks have been carried out and the VICH guidelines have been followed.

**STUDY CONDUCT**

As the reader will be able to deduce from the various chapters, study conduct varies for different species and different applications. The main objective should, however, be good teamwork. The careful selection of the investigator and the site prior to starting the study, including discussion with all colleagues of the department to ensure that the study plan is of a good design and scientifically meets the objective of the study, is of paramount importance prior to the start of the study.

Adequate insurance is something that must be undertaken, especially where the study site may involve racehorses or thoroughbred horses, as can be seen from the chapter dealing with clinical trials in equine species. Here, one unexpected Adverse Event can lead to many thousands of pounds being required in compensation.
The informed consent process is also extremely important, especially when dealing with the companion animal owner. Here we are dealing with a totally different person from the farmer. An accurate description of the study that a companion animal will be included in and the written consent of the owner is of paramount importance. The sponsor and the investigator should confirm that the owner(s) has full knowledge of what will happen to their favourite animal.

For the conduct of an effective clinical study to any good practice, let alone GCP, every member of the team needs to know what is required, have regular communications, be well trained and ensure that everyone is conducting the study according to the agreed study plan.

**FACTORS FOR SUCCESS**

Without taking any more time to discuss the conduct of the clinical study, which is adequately covered in the following chapters, I would merely draw your attention to other aspects that need to be in place to allow a successful study to come to fruition. Leaving aside good study design, compliance and all the other aspects required by VICH guidelines, there are five key factors for success which also need to be addressed by the sponsor and the site personnel.

**Commitment**

It is no good having a very good study design and being well aware of the concepts of GCP if the whole team is not committed to both the study and the objective. One of the prime reasons for conducting clinical trials from the investigator’s point of view is to increase standing in the scientific community and to hopefully review new scientific methods and trends which will be of benefit to the animal health fraternity in general, especially the target species.

**Resources**

Resources covers many areas—people, animals, equipment and, to a certain extent, money. Again, each of the chapters delves into these particular areas for the specific animal species under discussion. I would merely draw your attention to the fact that a lack of sufficient resources in a timely manner can only lead to delays, and delays can prove costly in registration.

**Qualified People**

The qualification of an individual is often immaterial to one's expertise. I would, however, not draw the line at pure academic qualifications but take qualifications as the fitness of a person to do the task for which he or she has been selected. Certainly, we need the qualified investigator, possibly both academically
and scientifically, yet a large number of the team members will not be academically qualified. They must, however, be qualified by regular working practices and be fully aware of not only the conduct of the clinical study but also educated by the investigator and the sponsor in GCP. Employing a person who has no basic knowledge of GCP but is an expert in a particular field, such as milking the cows, is detrimental to the project if the person is unable to translate that activity into one which will comply with GCP. The qualification of the personnel, therefore, is through a very detailed training session by the sponsor, the monitor and the Principal Investigator in not only the study conduct but also the compliance with GCP.

**Paperwork**

One of the critical changes that we have seen over the past 20 years with good practice is the vast increase in paperwork. Now we have first and second drafts of the protocol to meet everybody's requirements, rather than discussing the study design before committing pen to paper. Following that, amendments are frequently drawn up where good study design has not been thought out from the beginning. Standard Operating Procedures (SOPs), recording books and forms, telephone records and monitoring reports—the list is endless. At each stage of every clinical trial, there are documents that must be completed, signed and archived. This in itself can become a time-consuming operation.

For all members involved in conducting a clinical study, one of the most important tasks is to ensure that they are aware of the aspect of recording and "paper movement". Without everyone comprehending why it is necessary to sign and date everything and to make the same entry onto two or even three forms will result in either it not being done or done incorrectly.

One of the critical tasks that must be established with every clinical study is traceability and accountability through the audit trail concept. In other words, if a deviation from the required practice is made, then this must be written down. The U.S. Food and Drug Administration (FDA) has a wonderful phrase: "If it is not written down, then it has not been done". This message in itself is one that must be transmitted to the entire clinical team to ensure that the study can, at any time in the foreseeable or not foreseeable future, be reconstructed.

**Money**

Naturally, all of the factors for success cost money. Without monetary resources, many of these factors will not be put into place; therefore the quality of the clinical study will diminish. A balance between cost and benefit must be maintained. To conduct a study to the standards of GCP and then claim that it increases costs by 30 percent indicates that there was a poor level of science present in the first place. Compliance will increase costs, but often these are inflated erroneously by management to purchase new machines or facilities with
the false statement that they are required for GCP. This naturally undermines the concept of GCP; just because it is old does not mean it must be replaced. *If it is fit for use, then it is satisfactory.*

**CONCLUSIONS**

I hope that this introductory chapter has helped paint the picture as to the whys and wherefores of conducting clinical studies. For your specific questions to be answered, the appropriate chapter should be turned to, where you will find a wealth of experience to assist you in setting up and conducting your clinical study.

My main hopes and aspirations for the future of the animal health industry as it moves forward to GCP in veterinary animal health clinical studies are that there will be an inspectorate to make sure that we all operate to the required standard and that a directive is produced to give some teeth to the inspectors to make sure that every sponsor is conducting the appropriate clinical trial with the appropriate quality standards. The VICH document as it stands is an acceptable and usable document. This must, however, be transmitted on a worldwide basis so that the global conduct of clinical trials meets the internationally accepted standard. Whether a study is performed in the United Kingdom or in Brazil, we know that the data have been collected satisfactorily and that both studies have been conducted to exactly the same standard.
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USEFUL ADDRESSES

Animal Health Institute, 1325 G Street, NW, Suite 700, Washington, DC 20005-3104; Telephone: 202-637-2440; Fax: 202-393-1662

Society for Quality Assurance, 515 King Street, Suite 420,
Chapter 6. SETTING UP GCP TRIALS IN FISH


Chapter 7. SETTING UP GCP TRIALS IN POULTRY


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10 Chapter 10. SETTING UP GCP TRIALS IN CALVES


Chapter 12. Setting Up GCP Trials in Horses and Ponies


Chapter 13. GENETICALLY MODIFIED MICRO-ORGANISMS AND GCP STUDIES


Advisory Leaflet Number 4, Good Laboratory Practice and the role of the Study Director.


Chapter 17. THE GENERIC PROTOCOL

The protocol must be signed and distributed to all parties before the study starts. If further copies of the protocol are required, the original is drawn from the archive and the additional recipient's name included on the distribution list.

AMENDMENT TO THE FINAL PROTOCOL

Although the final protocol is intended to be the final document for the conduct of the study, some changes may have to be made as the study progresses. These changes will be planned, and there will be advanced notification of the proposed changes. All changes or modifications must be discussed and agreed on by both the investigator and the sponsor. An amendment is to be generated, providing reasons for the changes and what impact the changes will have on the study.

The amendment is to be signed by the investigator and sponsor and issued to all those on the protocol distribution list, notifying them of the change to the original protocol. An amendment must be distributed prior to the changes in the protocol taking effect. All amendments must be included in the final study report.

DEVIATION TO THE PROTOCOL DURING THE STUDY PERIOD

During the conduct of the study, a deviation to the protocol may occur. A deviation is a change to the protocol which could not be predicted, unlike an amendment.
ment which is planned. All deviations must be explained in writing and recorded by the investigator. All deviations which have an impact on the integrity of the study should be discussed in the final report.


ACKNOWLEDGEMENTS

I would like to thank all the investigators with whom I have had the privilege to work in conducting clinical studies to GCP. It is these investigators who have provided the material for this chapter. They have made it clear that if it is not in 182 Veterinary Clinical Trials from Concept to Completion the protocol, they will not do it and quite rightly so. However, on some occasions, if it is included in the protocol, it will still not be done. It is these investigators, who have not understood the protocols, who have taught me that the protocol must be perfectly clear with all details and instructions included, whom I thank.
Chapter 19. DATA, STATISTICAL ANALYSIS AND REPORTING FOR VETERINARY CLINICAL TRIALS


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