Veterinary Clinical Studies: Managing Expectations

Introduction
Clinical studies are a vital component of development and regulatory approval of veterinary medicines for the global marketplace. Success in obtaining authorisation to market a product is dependent upon demonstration that the product will work (efficacy) and will do no harm (safety), in the target population and under the conditions of intended use. In contrast to research-phase studies, which may provide a "reasonable expectation" of safety and efficacy, clinical studies for regulatory submission must "establish" safety and efficacy. This is accomplished in large part through valid study design documented in a comprehensive protocol. Generation of a high-quality protocol, however, is just one aspect of meeting the stringent regulatory requirements for establishment of product safety and efficacy. Follow-through is essential to provide assurance that the study is conducted according to the protocol, and ensure that the data collected are acceptable to the regulators.

The VICH, an agency for Veterinary International Cooperation on Harmonization of technical requirements for veterinary product registration, consists of three full member regions (EU, USA and Japan), as well as associate member regions (Australia, New Zealand, Canada and South Africa). The VICH published a guideline for the conduct of clinical studies, according to the principles of Good Clinical Practice (GCP). GCP is intended to be an international scientific quality standard for "designing, conducting, monitoring, recording, auditing, analysing and reporting clinical studies evaluating veterinary products". Compliance with this quality standard provides the regulators, as well as the public, with assurance of the integrity of the clinical study data submitted in support of product registration. The VICH GCP guideline number nine, GL9, was implemented in 2001; despite that, in 2014, it is still a significant challenge to conduct a clinical study comprising multiple sites spanning several regions of the globe that will satisfy, in all aspects of study conduct, all regulatory agencies in all of the various countries involved.

A common failing among animal health companies, including those with little or no previous experience of product registration, as well as some companies with considerable experience, is to underestimate the level of oversight and rigorous attention to detail required for successful conduct of a clinical study. This can lead to failure to dedicate sufficient resources, in terms of time, money, or personnel, to study planning and conduct, to the detriment of the product registration process.

Similarly, it is a common misconception that the "quality" aspect of clinical study conduct can be undertaken by other members of the R&D team, in their "spare" time. It is absolutely essential to employ, train, or contract specific expertise in GCP study conduct, to successfully register veterinary medicines. This unique skill set is rarely found to coexist in the same personnel who excel at other aspects of product development. Study scientists and veterinarians have skill sets that are complementary to, but quite dissimilar from, those of a GCP expert. Experts in conduct of studies to GLP (Good Laboratory Practice) standards, although they have training in "quality systems", are seldom cross-trained in GCP principles, as the two standards serve quite different purposes. An aspect of GCP study conduct that is unique to this type of study is the need for coordination and training of external collaborators, such as academic or veterinary specialists, who, although experts in their own field, often have little experience in working to established "best practices" in the area of clinical study conduct. Thus the procurement of experienced GCP study Monitors, and dedication of their time solely to conduct of clinical studies, is an important step toward establishing product safety and efficacy.

The GCP guidance defines the roles and responsibilities of the key study personnel, including the Sponsor, the Investigator and the Monitor. Provision is made for delegation of certain responsibilities to supporting study personnel, or external contractors. A complex multi-site study will involve a large number of Investigators, supporting staff at each study site, a team of Monitors, animal owners, dispensing pharmacists, product administrators, diagnostic laboratories, statisticians, veterinary specialists (such as oncologists, cardiologists, dermatologists), quality assurance auditors, data management personnel, and product shipping and distribution specialists. The regulatory agency may also audit study activities or documentation. Coordination of such a large team of disparate experts, often in different locations, and even different time-zones, is a major undertaking, and should not be underestimated. Successful study management requires a team of people with training and experience in GCP study conduct and can be a full-time commitment for all concerned.

The purpose of a clinical study is to evaluate the product performance under the intended conditions of use, that is, in the "field". This adds another level of complexity to study management, since the well-controlled conditions of a laboratory-type study are no longer possible. The ability of the study team to manage change is of critical importance in field studies.

Challenges Associated with Conduct of Clinical Studies

Trial Clearance Applications

Obtaining permission from regulatory agencies to conduct clinical trials requires patience and persistence. There is a decided lack of consistency among the member states of the EU with regard to the requirements for trial clearance applications. The nature and quantity of data required for support of quality, safety and preliminary efficacy of the product is member state-specific. The cost per application also varies significantly. A study protocol is typically required

as part of the application, however, there is a lack of consensus, particularly between the EU and USA, with regard to acceptability of inconsistencies between the protocol and the actual study conduct. Furthermore, it is not possible to predict the time required to obtain clearance, or even if clearance will in fact be granted. Regulatory agencies may respond to the application with a list of questions, or even with a request for additional data, thus extending the time required to obtain trial clearance. The potential for delays in granting of trial clearance should be made clear to all study participants, and in particular the Sponsor, from the outset, to avoid unrealistic expectations.

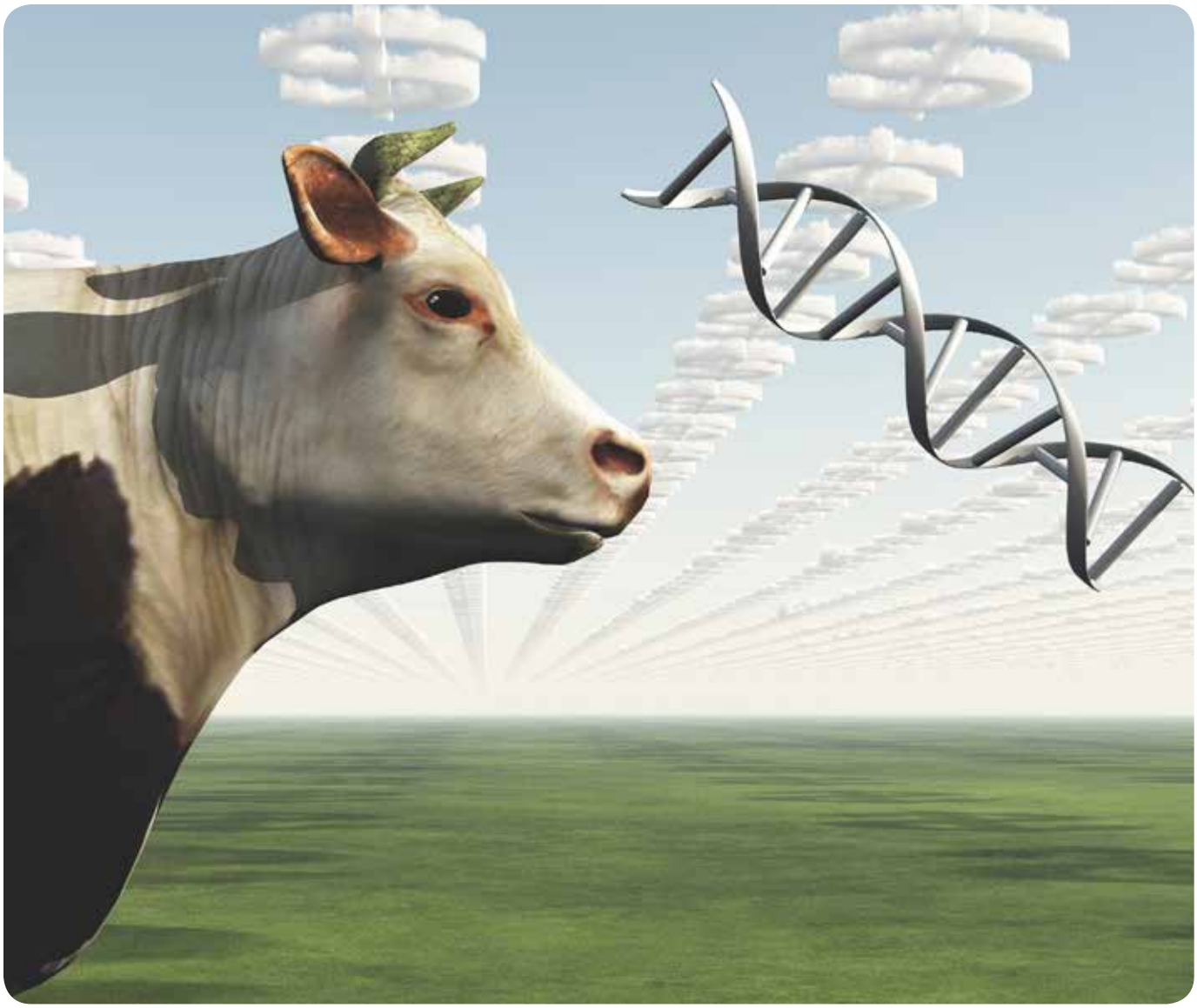
Availability of a Reference Product

Comparison of the efficacy of the investigational product to a negative control group may be advantageous from the scientific perspective, however, from an animal welfare perspective it may not be acceptable to leave animals untreated, depending upon the type of disease involved. In some cases, the study will aim to demonstrate equivalence or superiority to a product that is already on the market. Availability of the chosen reference product (to be used in the positive control group as an established comparator) can present a challenge. Different products are approved in different member states of the EU, and in countries outside the EU. Thus time must be allowed to obtain any required import permits, as well as regulatory permission to use the same reference product in all study animals.

Case Recruitment Rate

Recruitment rates are unpredictable and can vary significantly among farms/practices, geographical areas, countries and continents. There are many reasons for unsatisfactory progress in recruitment of cases, including a lack of animals presenting with the condition to be treated, or a failure of the animals that do present, to meet the study inclusion criteria. The study may be poorly-designed, such that the inclusion criteria are not realistic. The husbandry practices in certain geographical regions may limit the need for the specific type of product, or temperatures in a given region may be unseasonable, impacting disease status.

The unpredictability is not limited to the items above. The veterinary practitioners may not recommend the product, if it does not fit well with other aspects of their practice, or if they feel it may jeopardise their relationship with a client. The



animal owners may not choose to participate in the study, or may withdraw their participation part-way through the study. The study may be reliant upon an environmental challenge, which may simply not occur that particular year, despite the history of the region for outbreaks. All study personnel must be educated with regard to the risks inherent in conduct of studies in the "field", and a plan for overcoming such challenges must be considered in advance.

Limiting Protocol Deviations and Amendments

Clinical studies may involve 20 or more Investigators, often distributed across several countries and even continents. The Investigators may be specialists in a relevant therapeutic discipline. This makes it challenging to reach concurrence on aspects of study design and conduct, as the different experts may disagree on the best way to proceed, and clinics may follow different standards of care and treatment protocols. Consistency, especially in regard to scoring of any subjective outcome variables, across study sites, and even between personnel within a single study site, is a major challenge. Differences in judgement can have a major impact on the study outcome. For example, one observer may very diligently record every small transient reaction at the injection site, whereas another observer may consider such reactions a normal consequence of vaccination, and will not record any reaction. Such variability can be minimised by training of Investigators and other study personnel, so that all are aware that clinical relevance of all events will be determined during data analysis, and data should not be censored at the Investigator level.

Frequency and Reporting of Adverse Events that Occur During the Study

Clinical studies are often the first large-scale use of the product in the target animal. The expected safety profile of the product is based upon preliminary laboratory data, and the trial clearance has been granted based upon certain expectations. It is not unusual to find that a product performs differently than expected in the field (under the conditions of expected use). The challenge presented to study management personnel in this situation is how to collate and report adverse events for compliance with the trial clearance requirements, as well as compliance with current pharmacovigilance requirements. Pharmacovigilance is an area that would benefit from global harmonisation; efforts to this end are underway, but at present there seems little consensus within industry practices, with regard to the level and type of reporting of adverse events occurring in clinical studies.

Verification of Study Data After Collection

The study Monitor verifies the data collected throughout the study period, and following completion of the live phase of the study, the data are entered into an electronic database. Various editing checks and data validation protocols are applied, that can result in a list of data points that require confirmation and may involve a correction to the raw data record sheet. Such a correction may only be made by the Investigator, thus an additional visit to the study site by the Monitor will be required, sometimes months after the last collection of data. Further quality control techniques must be employed, to ensure verification of 100 % of the data that has been entered in the database.

The use of direct electronic data capture, using software compliant with the 21 CFR Part 11 regulations is becoming common, such that data entered and any changes to the data are tracked and attributable through the use of electronic signatures. A separate exercise of data entry is no longer needed; edit checks and validations are employed at the point of data entry, and this reduces the verification required. However, electronic data capture is not suitable in all field situations, and although operation is relatively problem-free in veterinary clinics, the method does not transfer well or reliably to the farm. In addition, opposition to electronic data capture is not unknown; it is a new concept for Investigators who may have already conducted several successful studies and are reluctant to change.

Quality assurance auditors will perform an independent, additional confirmation of the verified database by reference to the full data sets from 10 % of the study animals, whether the data has been collected manually or electronically. Following sign-off by the auditor, the database is locked, and is ready for statistical analysis.

Statistical Analysis of Study Data

The input of a statistician early in the study design and protocol development process is important, to ensure that the study outcome will support the proposed product indication(s). The planned statistical analysis must be described in the study protocol, including stating the tests to be used, and how the data meet the assumptions of those tests. The assumptions need to be justified by the nature of the response variables and study design. Interval estimation, rather than significance testing, is preferred, as the focus is on clinical relevance. The criterion for concluding whether the findings support the proposed product indication should be stated. However, conclusions should not be based on statistical measures which may accompany the estimate for the purpose of assessing its relative precision. For example, a 'p value' by itself is not a sufficient criterion to support a conclusion.

If changes to the planned analyses (as stated in the protocol) are necessary, justification must be provided and reasons for the changes given in the final study report. In effect, the risk of changing the statistical analysis at this stage is that it may lead to the regulators not accepting the data.

Writing the Final Study Report

Following the intense activity of completing a clinical study and sign-off of the data set for statistical analysis, there is often pressure to rush through the report-writing phase, to meet timelines for submission of the report either directly to the regulatory agency for review, or to those responsible for compiling the dossier for submission. After spending months collecting the data, it is important to do it justice at this point, by taking the time to write a high-quality study report.

Every aspect of study conduct must be fully described, and any deviations from, or amendments to, the study protocol, must be identified and justified and impact assessed. Post-inclusion removal of study animals must be fully explained and must follow the criteria stated in the study protocol. The inclusion or exclusion of any data from those animals, in the statistical analysis, must be fully explained and justified. This can be a point of contention in a multi-site study, and significant effort may be required to ensure that consistent rules are applied. The data and statistical analyses should be clearly and concisely presented, using figures where such illustration will contribute to clarity and understanding of the results. The study results should be fully interpreted in the "discussion" section, and conclusions should be drawn that are substantiated by the statistical analysis of the data.

Consequences of Delays at Any Stage of the Study - "Delay Leads to Delay"

Delays in obtaining trial clearance, or recruitment of cases at a lower rate than anticipated, can be further exacerbated by expiry of import permits prior to shipment of investigational product, or by expiry of product that has already been shipped to study sites. Additional time is then required to obtain new permits or ship additional product. Product supply may also become an issue, if multiple shipments are required to several sites. Availability of animals can become limiting, for instance, if young animals are required and study initiation is delayed until later in the season (for seasonal breeding animals).

The combination of delayed activities around the time of study initiation, as described above, and the considerable amount of time required after completion of the animal phase of the study, for verification of the study data and report-writing, can quickly add up. Completion of the clinical study report is often the last stage of dossier preparation, determining the timing for submission to the regulatory agency. Delays at this stage impact the product launch date, resulting in a loss of sales, potentially a missed window of opportunity for sales if the product is indicated for a "seasonal" disease, and can even result in loss of the coveted "first to market" status of the product. Thus there are many important reasons to avoid delays in clinical study completion.

Strategies for Minimising the Impact of the Challenges Inherent in Clinical Studies

Advance Planning

A reasonable period of time must be allocated for study planning and logistics activities. Pre-study planning is not limited to protocol development. Planning involves ensuring that investigational, control, and reference products are available to all study sites, during a specific window of time. This window is a moving target, as it is not possible to predict the outcome of trial clearance and import permit applications. Thus it is necessary to plan for several eventualities, such that delays in product supply are minimised. A significant amount of planning is associated with provision of sampling supplies to study sites, preparation of study documentation (hard copy, or electronic data capture systems), training of study personnel, and putting contracts and agreements into place. Adequate advance planning is the most effective way to minimise the impact of circumstances that are not controllable, such as the weather, the season, disease outbreak timing, Investigators with conflicting commitments, and other unforeseen events. Compressing the time-lines in this critical phase of the study is counter-productive, as it can lead to the necessity for very costly and time-consuming recovery measures at a later date. Building a functional study team begins with defining criteria for selection of study sites, Investigators, data management personnel, and third-party participants, such as testing laboratories or product shipping/distribution contractors. Such criteria include finding laboratories and product distributors employing appropriate quality standards, and compliance with relevant regulations, such as 21 CFR Part 11, which pertains to electronic data capture regulations. The team-building phase may involve auditing and inspection of facilities, to qualify any vendors; this may necessitate the involvement of quality assurance personnel. The process of selection is time-consuming, but critical, as the study outcome is dependent upon the expertise of the team assembled.

Selection of study Investigators is an art. There are some obvious criteria they will be expected to meet, such as access to suitable cases, interest in the project, specialist expertise available, and appropriate facilities. Key opinion-leaders and experts in the relevant field are often targeted, as they lend credibility to the study. The role of Investigator requires a significant commitment of time, for completion of documentation, liaison with other study personnel, participation in meetings and training sessions, and conduct of Monitor and potentially auditor (regulatory agency or quality assurance personnel) visits. In addition, the Investigator is charged with inventory control, secure storage, and temperature monitoring, of the reference, control, and investigational products. Records must also be maintained of disposition of all study animals, and in the case of food-producing animals, assurance must be provided that the assigned withdrawal period has been adhered to.

It must be recognised that the sheer volume of work involved with the role of study Investigator precludes combination of the role with a concurrent full practice load. It may be more effective to appoint an alternative veterinarian at the same practice to fill the role of Investigator, and define the role of the expert as an advisor to the study. To make such decisions, an in-depth understanding of the responsibilities of the key study personnel, and the time required to complete those activities, is essential. Such knowledge comes only with experience.

Communication

The study Monitor, or more often the team of Monitors, is responsible for study planning, coordination and facilitation, from inception until issue of the final study report. During the live phase of the study, the Monitor, Investigator, and Sponsor are in constant communication, regarding recruitment progress, adverse events, cases lost to follow-up, protocol deviations, administration of concomitant medicines, and laboratory results. This is a large volume of communication when the study involves multiple sites; short-notice visits to

the sites by the Monitor may be required should an event arise (disease outbreak, environmental challenge experienced). Communication should be prompt and detailed, with clearly defined communication channels. A single point of contact (with back-up coverage) is recommended for key aspects of study management. Communication of all aspects of the study to the Sponsor is a key responsibility of the Monitor; this includes ensuring that the expectations of the Sponsor are realistic and achievable in terms of timelines and study outcome.

Engagement of the entire study team from the planning phase onward is essential. Decisions made in isolation often lead to problems later on. For instance, it is important to consult clinic or farm staff, and to take into consideration their normal operating procedures, when defining activities such as treatment administration or sample collection. This is not to say that an unwieldy system of review of all decisions by every study participant should be adopted. Responsibilities of all study personnel should be well established. Only experience can define the line between insufficient communication, and over-communication to the detriment of progress.

Training the Team

Detailed training on the study protocol and data collection system is essential. All study participants must be fully informed of all safety and efficacy testing of the product to date. This information can be provided in the form of an Investigator brochure, but it benefits from presentation during training sessions as well. It is important to ensure that the Investigator, clinic or farm staff, and treatment administrators, receive training on the study protocol, as well as training in the principles and practical implementation of GCP. The regulatory agencies review the study documentation for GCP-compliance, and may also audit the live phase of the study, or audit the study site after completion of the study. The consequence of non-compliance can be rejection of the study report by the regulator, necessitating a repeat of the entire study, requiring significant expenditure of both time and money.

Recognition of the Reliability of Resource Estimates

Clinical studies are subject to the vagaries of nature, and more subject to the whims of man, than laboratory studies. It seems reasonable that the Sponsor should be fully prepared for potential escalation of both time-lines and costs. In reality, there are equal and opposite forces exerted to temper the propensity to provide the "worst-case" time and cost estimates. Regardless of whether the bearer of tidings is the head of clinical development reporting to the head of R&D within a given company, or the representative of a clinical research organisation providing a cost estimate to a prospective client, the dilemma is the same. Presenting the worst-case time and cost estimate, or even a realistic mid-range estimate, will often lead to cancellation of the project.

It seems counterproductive to depend on an unrealistically-optimistic estimate. Yet presenting a brutally honest estimation of the likely costs may well result in transfer of the funding to a project with less chance of success (i.e. with an optimistic/unrealistic budget), thus the best interests of the company have not been served. Such an estimate of costs provided by a clinical research organisation to a prospective client can lead to loss of the contract, and placing of the contract with a less-principled (or simply less experienced) organisation, with the outcome that all cost and time-lines are over-run, often beyond the point of the competing tenders. This dilemma is not unique to the animal health industry; it exists in many sectors, including building construction, IT and manufacturing concerns.

A solution may be to present both ends of the cost/time continuum, providing estimates for a study that proceeds with no unexpected costs or delays, as well as for the worst case, where maximum time and costs are encountered. This type of presentation would need to be combined with education of the Sponsor with regard to the risks that are inherent in clinical study conduct, and the ways in which the risks can be mitigated

Conclusion

There are many aspects of clinical study conduct that are unpredictable. The most effective countermeasures against the tendency toward chaos are assembly of a highly-experienced team, and provision of the resources necessary to accomplish the goal, that is, establishing safety and efficacy of the product in the field, to the satisfaction of the regulators, and ultimately, authorisation to market the product.

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