Is it Safe & Effective? Clinical Studies Evaluating Veterinary Medicines: *Increasing Focus on High Quality and Representativeness*

This is the third article in the "From Molecule to Market" series, where the challenges to successfully run a clinical program for the registration of new veterinary medicinal products shall be described. While traditionally all safety and efficacy studies conducted in the target animal species are considered "clinical studies", the European Union (EU), lately, has introduced a more restricted definition of "clinical" studies being the pivotal field efficacy and safety studies only. In this article we will focus on the field studies, while providing some considerations for pre-clinical studies as defined now in the EU.

Introduction

To obtain marketing authorisations in Europe, the US and most other areas of the world, the safety and efficacy of a product requires to be tested in the target animal and indication in controlled studies. These studies need to be conducted to the current state of veterinary medicinal scientific knowledge and need to comply with regulations and the scientific guidelines related to quality, safety, and efficacy of Veterinary Medicinal Products (VMPs) as published by US-FDA, EMA-CVMP, in monographs like Ph.Eur. and USP, OECD-/FDA Code of Federal Regulations, and VICH-GCP standards. Obviously animal welfare standards need to be applied to all studies, and where applicable, in case of release of VMPs containing Genetically Modified Organisms (GMOs) further regulations may apply. Additional further guidance(s) exists for different kinds of studies, many published by VICH and thus applicable for both the EU and US (e.g., VICH GL41 and 43 on Target Animal Safety). Guidance published by the individual regulatory bodies (FDA-CVM and DVMP) also exists on specific indications for different target animal species for their respective countries. Scientific bodies add relevant guidance as well (e.g., WSAVA.org, WAAVP.org). There is a legal definition of veterinary clinical studies published in the European legislation, and this article focuses on such clinical trials:

Definition of clinical and pre-clinical trial (study) based on Regulation (EU) 2019/6

'clinical trial' means
a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof

'pre-clinical study' means
a study not covered by the definition of clinical trial which aims to investigate the safety or efficacy of a veterinary medicinal product for the purpose of obtaining a marketing authorisation or a change thereof

Prior to planning any pre-clinical or clinical studies, the exact identity, and specifications of a product must be established. A well thought out series of *in vitro* and, depending on the intended plans, *in vivo* studies in non-target animals should be performed, before administering any product under field conditions to client-owned animals. A development plan, based on good scientific understanding of the attributes of the active ingredient and product will be of utmost importance to de-risk the development of any product, but also to minimize the risk to the target animal as much as possible, when a complete dataset of studies is not yet available.

Planning the Conduct of Pre-clinical and Clinical Studies

To plan and conduct pre-clinical and clinical studies in the target animal species, a good team of experts should be consulted utilising individual experts to cover different topics. This includes but may not be limited to the experts as listed in Table 1a. Studies typically falling under the definition of pre-clinical studies are listed in Table 1b).

Table 1a: Experts to be involved
Sponsor representative
One or more expert veterinarian(s), potentially serving as investigator(s) or study director in the indication targeted
Well trained clinical monitor(s)
Experienced statistician used to work in animal health
Quality Assurance Unit
Expert in clinical supplies incl. labelling, logistics, ex-and import between third territories
Clinical and/or analytical laboratories

Table 1b: Pre-clinical studies
Proof of concept studies
Pharmacokinetic studies
Studies testing a product under a well-established model for effectiveness
Dose finding/escalation studies
Dose escalation studies
Dose confirmation studies
Target Animal Safety studies
Residue studies
Other laboratory-based studies to evaluate effectiveness or safety in target animals

Animal Test Permits (ATCs)
Depending on the territory or country where a study shall be conducted, test permits may be required. In the EU, Regulation (EU) 2019/6 mandates the National Competent Authorities (NCAs) grant such permission within 2 months after all information has been provided by the applicant. The information that needs to be provided to NCAs for studies to be conducted in the field are included in Table 2. ATCs are not required in the US; however, an Investigational New Animal Drug (INAD) file should be established with the FDA-CVM prior to shipping drug for use in any studies to be done in client-owned animals. Special attention should always be considered for consumer safety: a withdrawal period must be set by the NCA prior to any product or tissues deriving from such study animals to reach the consumer for food consumption. In the US, FDA-CVM will set such limits.

Table 2: An excerpt of requirements for test permits in EU for veterinary field trials

Details/Info* on:
- Applicant, Administrative information, as part of application
- List of qualified participating investigators in the country of conduct**
- Active Substance (API)
- Start and End date
- Draft Summary of Product Characteristics (SPC)
- Pharmaceutical form and route of administration
- Dosage regimen
- GMP for the manufacturer of the Investigational VMP (IVP)**
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- List of countries where the IVP is authorised/ registered already
- Data on handling and storage, composition on ingredients, physical and chemical properties, toxicological and pharmaceutical data on IVP
- Specific measures relating to the prevention of the transmission of animal spongiform encephalopathies (TSE statement)
- Target species and indication targeted
- VICH-GCP compliant study protocol incl. statistical plan
- Compliance with VICH GL9 (Good Clinical Practice)

Control/Reference product:
- Justification of choice
- Name, SPC and package leaflet of the control product used
- Labelling, logistic partner, GDP compliance

In case of Food Producing Animals (FPA):
- Summary report of the CVMP concerning the product (MRL)
- Summary report to MRL data of sponsor
- Summary report to MRL of CP
- Residue study, if available
- Proposal and justification for a withdrawal time (if applicable in food producing animals)

*Requirements may vary from country to country
**Argenta/Klifovet can act as such, holding the relevant licenses

Quality of IVPs and Import From Other Countries
In the EU and the US, IVPs tested under field conditions in pivotal studies should be manufactured to represent the product intended to be registered and commercialised. To assure the appropriate IVP is used, more and more competent authorities in the EU require that such products are produced in facilities that are certified to be GMP compliant for these kinds of products. In the US, IVPs used in pivotal studies should be manufactured to current GMP standards in facilities that would be expected to pass GMP audits by FDA.

Where field studies shall be conducted in the EU with a product produced in a 3rd territory or country, such products require to be imported to the country where the study shall be conducted: an organisation importing such product has to hold an import license for VMPs, must be located in the EU, and takes responsibility for the product by releasing it for use; they can ship "released" clinical supplies to the target country within and outside the EU, where a test permit has been granted; logistics should follow the principles of Good Distribution Practices (GDP). Typically, to obtain an import license will take about 2 months. In some countries, an import license is granted based on the granting of a test permit for such a study: this applies currently for the UK and Ireland. Information required for a test permit is listed in Table 3. In the US, no import license or test permit is required; however, FDA-CVM should be notified of the importation through a Notice of Import letter with details regarding specifics of the IVP and the port of entry into the US.

Table 3: An excerpt of requirements for importing vet. clinical supplies to EU for field trials

Import from 3rd territories* where Mutual Recognition Agreement for GMP inspections in place for that product group:

- Flow chart of manufacturing incl. all parties involved
- Certified importer for VMPs (GMP for manufacturing and import)**
- Valid GMP certificates from all parties involved in manufacturing of product in 3rd territories and within EU
- Audits conducted on all parties involved in manufacturing (within last 3 years)
- SPC, MSDS
- Active substance manufacturer incl. GMP compliance
- CoA and other information on the product/batch to be imported incl. quantities
- Further information on the product to be imported as listed above for test permits

*Requirements may vary from country to country
**Argenta/Klifovet to hold such licenses

Study Design
Pivotal clinical field studies tend to be the last and most expensive part of the development of a new VMP. Therefore, the information generated previously needs to be considered and will influence the objectives and design of a study for determining efficacy/effectiveness. A typical study design includes the core chapters of a protocol according to VICH GCP (Table 4).

Based on the authors experience, the most critical issues to develop a study protocol tend to be the inclusion criteria, exclusion criteria, and the clinical endpoints to be assessed. Wherever possible, validated methods should be applied, especially for primary effectiveness criteria.

As the focus of product development shifts further to geriatric and chronic indications in pets (atopic dermatitis,

Table 4: Study Design
Title
Justification and objective
Schedule of events
Study design
Animal selection and management
In- / Exclusion criteria
Treatments: Test and control product
Disposal of study animals, their products and IVPs
Assessment of efficacy
Define endpoints, how to measure and record
Describe analyses/tests to be performed
Select and define scoring system and measurements
Define methods of computing and calculating the effect
Adverse events
Handling of records
Statistics
Supplements
SOPs for conduct, monitoring, and reporting of study
Listing of raw data
Any other data of relevance
Instructions for amendments and deviations

allergies, oncology, heart/kidney disease), clinical field studies are essential for demonstrating various indications as challenge models or specific herds of animals with disease are missing and only "freshly" observed cases with no similar pre-treatment are required to assess the efficacy of such products mostly on rather subjective scores. This tends to be a real challenge for all involved, the investigators, the sponsors/investors, and the regulators who must evaluate such studies. Early field studies are required to de-risk such products in certain indications, but in many areas of the world, the feasibility to conduct such studies is limited due to national stringent legal requirements, who by themselves, pose a restriction to the best care of animals, as they cannot be tested and made accessible for animals.

Due to the extensive documentation requirements, the workload of investigators in clinical studies is usually high and intensive. After thorough training, most important is the identification and selection of the cases with the target disease, followed by performing the regular observations per

protocol, communication with the study monitor, managing adverse events, audits by QA, and inspections by competent authorities. Based on the current post-COVID setting, time is the most limiting factor in veterinary practice. Thus, new technologies are currently introduced (e.g., decentralised studies, direct owner relationships, telemedicine); electronic data capture, electronic informed consent and signatures have been implemented as standard tools for many studies. However, the technological hurdles (e.g., validation of hard- and software, internet access in remote areas, acceptance by investigators / study directors) are still existing and need further consideration; one reason why many studies in food producing animals still use paper-based data capture before entering the data to databases for analyses.

Beyond regular monitoring prior, during and after the study, audits by Quality Assurance may be implemented by the sponsor at critical time points, and potentially by the competent authorities in the US; also more recently, some NCA in the EU started to perform inspections at study sites during or after the study to check for compliance, correctness and integrity of a study. It is the sponsor's responsibility to assure that a thorough study report is prepared based on the statistical analysis and endpoints as described in the study protocol. Finally, all documentation, paper based or electronically, must be compiled and archived to allow review of such a study any time, until 5 years of expiration of the marketing authorisation, where such study was used for.

With Argenta Clinical based in NJ, US and KLIFOVET, based in Munich, Germany, Argenta Global is well positioned in the two most important animal health markets worldwide. The scope of services includes planning, study design, conduct and reporting of studies, but Argenta is unique in also offering all adjacent services including regulatory consultation, application for test permits, monitoring, data management, quality assurance, import and labelling of IVPs, purchase and labelling of control products, and reporting in a format "ready to submit", all this handled by experienced project managers.

Conclusion

The term Clinical Studies is defined as clinical field studies in the EU, either for safety or effectiveness. Marketing authorisations are granted on a positive benefit: risk balance. Therefore, clinical field studies are of utmost importance to provide such benefit. Thorough planning, experienced personnel, high quality conduct of such studies under well-defined conditions are the pre-requisite to be successful at the end of the development cycle of new products, even in the presence of high financial pressure. Therefore, it is of high importance to work with highly experienced experts as available at KLIFOVET and Argenta Global.

REFERENCES

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5. VICH: www.vichsec.org
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