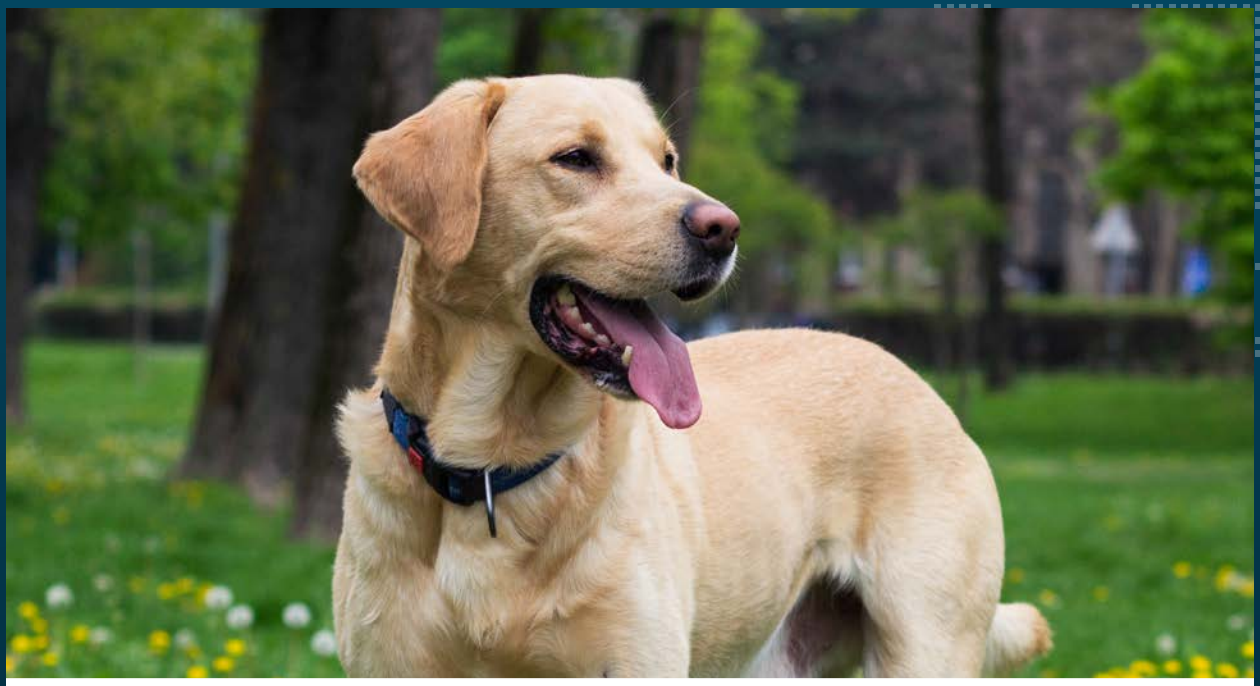

Terminology Matters: Understanding the Differences in Animal vs Human Drug Development

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Produced by:
Kisaco Research

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Introduction

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In the United States, human drug development is regulated by the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). For many people it comes as a surprise that the FDA also regulates drugs for animals. When I talk about the development path of drugs for animals, people are often amazed at the rigor required to achieve a New Animal Drug Approval (NADA) by the FDA Center for Veterinary Medicine (CVM).

Even among those that are aware of the CVM requirements for animal drug approval, often there is only a rudimentary understanding of what is involved. I believe that the terminology many of us in the animal health industry use to describe various aspects of the stages of drug development are confusing and contribute to why human drug developers do not understand the advantages we have in animal health: early evaluation of risk and the high rate of success in pivotal animal clinical trials compared to Phase III human studies.

Terminology commonly used on the human health drug development path is often misused when applied to animal health. This terminology gets in the way of investors and companies that are familiar with human health in understanding fundamental differences in animal drug development. These terms are ***preclinical*** vs ***clinical*** and the designation of clinical trials as ***Phases I, II and III***.

Pre-Clinical vs Pilot Laboratory

For human drugs, the CDER regulators want to assure that before a drug goes into any human being for testing, it has been extensively evaluated in laboratory animals. To oversimplify, requirements are the use of a rodent species (rats or mice) and one larger mammalian species, most commonly dogs, for toxicological evaluation. These studies attempt to predict possible toxicity in humans. Details of the design, cost and length of these pharmacokinetic, metabolism and toxicology studies vary depending on the drug, but generally once the pharmacokinetic profile is defined for each species, the compound is administered at multiple dose levels over a minimum of 3 months, and often much longer (9-12 months). Other studies, such as carcinogenicity and metabolism studies may be required. Experiments may be done using rats or mice as models of the drug action. These studies in laboratory animals are called ***pre-clinical studies***. That is, before testing in humans. Once these studies have been completed, data are analyzed and submitted to the FDA CDER for review. If the CDER reviewers determine the data are sufficient to indicate the drug is safe to be tested in humans, they issue an Investigational New Drug (IND) number and human studies can proceed.

For animal health drugs early development is very different. Some rodent studies may be completed early on, for basic safety, or perhaps rodent models of the intended label claim, but often most of the pharmacokinetics and early stage safety is done in what animal health drug developers call the 'target' species. That is, the species in which the drug is ultimately intended to be used. An example would be a drug intended to treat pain can be tested initially in laboratory dogs under controlled conditions for pharmacokinetics, bioavailability and safety information. In fact, these studies are clinical studies, in the sense that they are the first studies in the target species, unlike pre-clinical studies for human drug development. Unlike in human drug development, we don't have to hope the pre-clinical studies in one species will predict what will happen when the drug goes into another species.

"What seems like a semantics point actually is more—in fact, there is an important difference hidden in this terminology."

As many pharmaceutical companies know, they can spend years and many millions of dollars on ***pre-clinical*** studies in rats, mice and dogs trying to predict how a drug might behave in humans, only to find out these studies in fact do not predict human safety, metabolism, bioavailability or efficacy. Humans may have a unique toxic metabolite, for example, or bioavailability may be significantly different. After years of work and millions of dollars to achieve an IND from CDER and move into the target species (humans), the drug can fail.

We in the animal health drug development world have a major advantage. We work directly in the target species. The data we generate from our first studies is directly applicable to our future patients. This allows us to de-risk compounds prior to investing large amounts of capital. We can work with any target species—dogs, cats, horses, cattle, swine, poultry, in a laboratory setting or in facilities that mimic commercial operations. To highlight this advantage in animal health drug development, we should call these early laboratory studies in target animals ***pilot laboratory studies:*** pilot pharmacokinetic studies, pilot safety studies. These experiments are distinctly different than the pre-clinical studies conducted in human health drug development.

Another advantage in animal drug development is that the CVM will issue an Investigational New Animal Drug (INAD) designation without the submission of any data, because the CVM understands that we do our first work in the target animals and there is no need for extensive rodent data to evaluate prior to moving into pilot dogs studies. The application for an INAD number can be as brief as a couple of pages, describing the drug action and potential label claim.

Animal health drug development can be de-risked much earlier than human drug development and an INAD may be opened with this simple request, allowing critical discussions with the CVM regarding the proposed scope of the project. In order to highlight these differences, I propose dropping the words ***pre-clinical*** from animal drug development programs and replacing them with ***pilot laboratory*** studies.

Phases I, II and III vs Pilot and Pivotal Clinical Trials

In early animal drug development, test articles can be studied in client owned animals, as long as a sufficient safety profile has been established. Veterinary clinical investigators must have enough safety data to be comfortable enrolling their patients in a pilot study. The CVM does not require any specific safety data prior to initiating a ***pilot clinical*** study in client-owned animals.

These ***pilot*** studies can serve as go/no go checkpoints in a program and are also useful in providing data to support developing the protocol for the ***pivotal*** effectiveness study. This is to the advantage of the animal drug developer, because if the therapy does not perform well in actual patients in a ***pilot clinical*** study, the program can be discontinued early, significantly reducing risk.

Once positive pilot study data are in hand from a well-designed, properly powered study, the likelihood that the pivotal clinical study required by the CVM will fail is low. In fact, in animal drug development, it is rare for a pivotal study to fail.

Contrast this to human drug development where ***Phase I*** may involve a small number of healthy subjects, or subjects with the disease condition where both safety and dose are evaluated. In ***Phase II***, several hundred patients will be evaluated for safety and effectiveness. In ***Phase III***, thousands of patients are evaluated for a year or more in two separate studies for safety and effectiveness. ***Phases I, II and III*** take many years, and the risk of failure in ***Phase III*** is well known in human drug development.

If animal health uses the term ***Phase III*** for a pivotal clinical study, it may be confusing to those unfamiliar with CVM requirements. ***Phase III*** requires two large (several thousand), well controlled, human patient trials, while only one ***pivotal study***, with several hundred veterinary patients is generally required by the CVM. Further, Sponsors know the CVM does not use the ***Phase I, II and III*** terminology for regulatory filings.

Conclusion

We can better understand the risks and challenges of animal drug development if we use terminology that clarifies the difference from human drug development. Drugs for animals can be tested in the target species very early in development, and the fact that these therapies can move into client-owned patients early in development means that Sponsors can move ahead quickly with promising treatments.

Just as important, a Sponsor of an animal drug can know when to kill a program early in development when negative data are generated, limiting investment in a program that is unlikely to succeed.

"I suggest we move away from using human drug development terminology for animal drug development. This will help our communication about animal drug development to clarify the unique risk/reward proposition of achieving regulatory approval of innovative products."

Comparison of Terminology for FDA Regulatory Review of Animal and Human Drugs

STAGE	ANIMAL DRUG DEVELOPMENT	HUMAN DRUG DEVELOPMENT
Rodent, canine and/or primate studies of toxicity, pharmacokinetics, metabolism	Not required	*Pre-clinical studies* Multiple years of dosing in two species to attempt to predict performance in humans
FDA permission to initiate program	INAD –no data submission required	IND – submission of data from rodent, canine and/or primates; requires CDER review to proceed
Evaluate dose, bioavailability, safety	Pilot laboratory studies in the target species	*Phase I study* in healthy volunteers, or patients with the disease condition
Evaluate safety, effectiveness in patient population	Pilot clinical study	*Phase II study* in human patients
Evaluate safety, effectiveness in larger patient population	Pivotal clinical study in a larger number of animals depending on species and disease condition. For companion animals, approximately 300 animals are enrolled in one study. (Only one study required.)	*Phase III study* in human patients (several thousand) – two large controlled trials are required.