

## Regulatory Framework for Approval of New Animal Drugs in United States

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Publication Date: 23 February 2017

Article Link: <http://scientific.cloud-journals.com/index.php/IJAVST/article/view/Sci-534>



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**Abstract** Animal healthcare is a booming market catering needs of several companion and production purpose animals. Animal drug approval process in the United States (US) involves submission of an Investigational New Animal Drug Application (INAD), followed by submission of New Animal Drug Application (NADA) to the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM). Although regional variations are present in the regulatory process for veterinary healthcare products across the globe, harmonization initiatives like International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH) are playing a vital role in the veterinary medicinal product registration process by availing detailed guidance documents. The current article focuses on the regulatory requirements for new animal drug registration in the US.

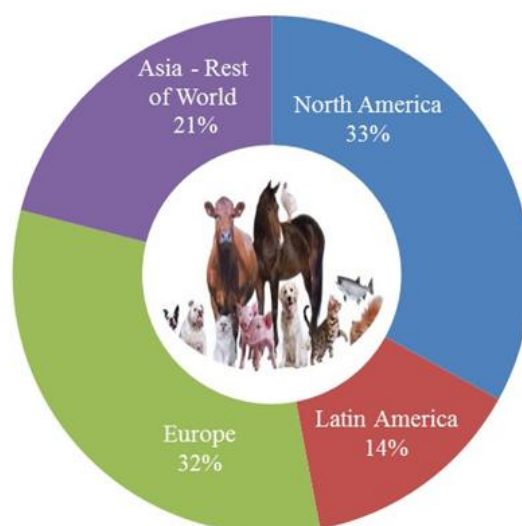
**Keywords** *US FDA; CVM; new animal drug approval; INAD; NADA*

### Introduction

Over the past two decades, global animal healthcare market has captured attention of top global pharmaceutical companies. This is because once a product is approved for human use then it is easier to expand the market share of the product by extending its usage in the animal health segment. Animal healthcare industry is exhibiting an accelerated growth potential. The global animal healthcare market, estimated at \$25 billion in 2015, is set to reach \$39.7 billion by 2021, with a compound annual growth rate (CAGR) of 8.06% [1]. According to Vetnosis, a leading research and consulting firm specializing in global animal health market, shares of animal healthcare sector are primarily distributed in the West where, 47% of the market is based in the US, 32% in the Europe and 21% in the rest of the world (Figure 1) [2]. The most valuable type of product by far is pharmaceuticals (62%), followed by biologicals (26%) and medicinal feed additives (12%) [2].

Rising global population, increased incomes and scarcity of agricultural lands have resulted in swelling demands for protein rich food items originating from livestock animals which include both beef and dairy cattle, pigs, sheep, goats, horses, mules, asses, buffaloes, and camels. With growing

urbanization, there is a rise in popularity of pet ownerships and growing human-animal bond. According to National Pet Owners Survey report, 65% of the US households or about 79.7 million families own a pet [3]. Apart from these, increased risk of developing age-related disorders in pets, increasing prevalence of zoonotic diseases (diseases caused by viruses, bacteria, fungi and parasites), the government initiatives worldwide on animal healthcare along with augmented global trend of large-scale farming practices are resulting into requirement of effective disease prevention and health management strategies. This is leading to constant requirement of good quality drugs, vaccines and nutritional supplements. Animal health companies are well equipped to address all these needs.



**Figure I:** Animal healthcare market segments: Geography wise

The US animal healthcare market, estimated at \$4.83 billion in 2016, is set to reach \$6.10 billion by 2021, with a CAGR of 5.22% [4]. The animal healthcare products in the US have been categorized into pharmaceuticals, bio-pharmaceuticals and veterinary devices.

### The United States Regulatory Bodies for Animal Healthcare Product Approval

As illustrated in Figure II, regulatory agencies for animal health products approval in the US include the US Food and Drug Administration's (US FDA) Center for Veterinary Medicine (CVM), the US Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) and the Environment Protection Agency (EPA). Whilst the US FDA's CVM reviews animal drugs and devices, the USDA does assessment of animal vaccines and biologics applications, whereas the EPA plays a role in regulating topical compounds against fleas, ticks and other parasites.

The CVM ensures that only high quality, safe and efficacious animal drugs reach the animals and consumers of byproducts. It also safeguards the food items derived from treated animals. CVM's responsibilities are handled by six offices, including the Office of New Animal Drug Evaluation (ONADE), which reviews information submitted by sponsors for obtaining manufacturing and marketing approval for animal drugs, and the Office of Surveillance and Compliance (OSC), which conducts post-marketing monitoring of animal drugs.

### Animal Drugs

In US, there is no discrete definition for animal drug. The Federal Food, Drug, and Cosmetic Act (FFDCA) defines the term "drugs" as "articles intended for use in the diagnosis, cure, mitigation,

treatment, or prevention of disease in humans or other animals” and “articles (other than food) intended to affect the structure or any function of the body of humans or other animals.”



**Figure II:** Regulatory bodies for animal healthcare product approval

In US, the target species for animal drugs are segmented into **major** and **minor** categories. Under major species category, there is a sub-division as companion animals (e.g. dogs, cats, and horses) and food producing animals (e.g. cattle, pigs and chickens). Under minor species, fishes, ferrets, goats as well as all the other animals apart from major species are included. The production animal segment drives almost 59% of the sales with the remainder driven by the companion animal segment [2].

### Scientific Assessment of Animal Drugs

Irrespective of variations in regulatory framework across regions, the basic rule of animal drug development includes scientific assessment of animal drug followed by its registration and upon receipt of approval from relevant regulatory bodies, finally marketing of the product.

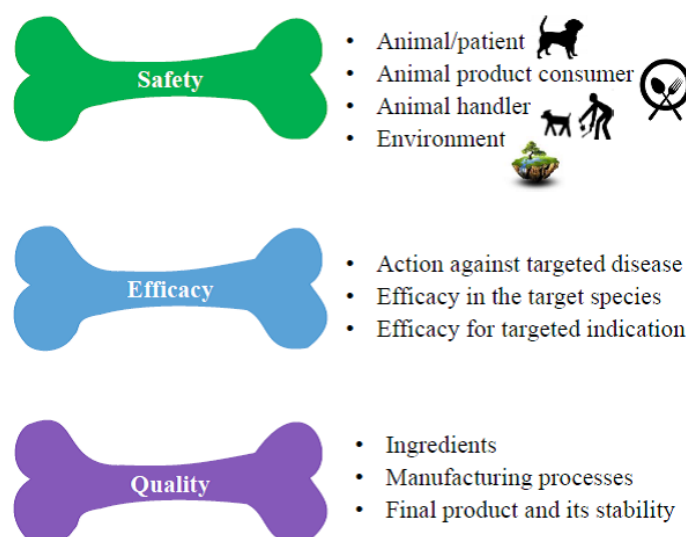
During scientific assessment, the biopharmaceutical company needs to ensure that adequate information pertaining to safety, efficacy and quality of the test drug has been collected as per the regulatory requirements (Figure III).

Unlike safety assessment of human drugs, veterinary drug safety assessment includes not only patient (animal) safety but also **food consumer safety** (the drugs targeted for food producing animals).

Besides this **handler safety evaluation** is required for assessment of safety of the people those will work with animals or have significant contact with animals. In addition to food consumer safety and handler safety the health authorities also require the submission of an **Environmental Assessment** (EA) or a claim of **Categorical Exclusion** (CE) for environment safety assessment.

For efficacy assessment, effectiveness of the test drug is tested in the target species, in the targeted disease or the targeted condition.

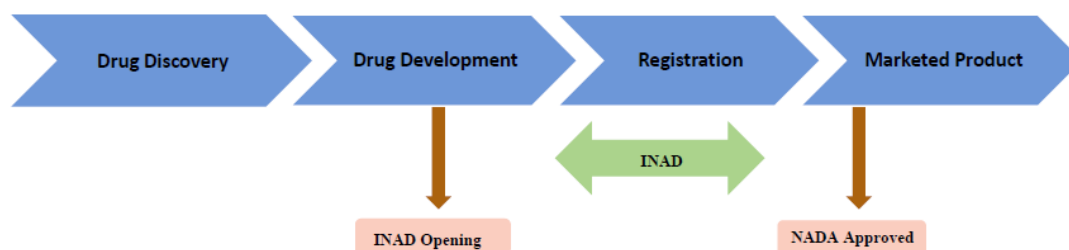
Quality assessment includes testing for ingredients, manufacturing procedures and facilities, purity and stability of the final formulation, maintaining batch-to-batch consistency in the finished products etc.



**Figure III:** Scientific assessment of animal drugs

### New Animal Drug Registration Procedure

Upon conducting market assessment for unmet animal needs, availability of business opportunities and completion of preliminary screening of new drug in the discovery and development stage, if the biopharmaceutical company decides to go for more expensive registration phase, the company needs to submit a letter to the ONADE of CVM to open an Investigational New Animal Drug Application (INAD) file and to initiate the drug registration process. As a part of the development plan, the ONADE and the drug sponsor need to discuss on the information needed to get the drug approved, including the number and types of studies that may be required and the overall design of each study [5]. A clear flowchart of the new animal drug regulatory approval process is illustrated in Figure IV.



**Figure IV:** New animal drug development process

The INAD file allows shipment of the drug for use in the studies and may authorize the use of edible tissues from animals treated with the investigational animal drug. Upon establishment of the INAD file, the sponsor plans and conducts the studies needed to support approval. Registration requirements for approval are categorized into seven technical sections, out of which five are major viz., target animal safety, effectiveness, human food safety, chemistry, manufacturing, controls, and environmental assessment, whereas two are minor technical sections viz., product labelling and all other information.

Under the 'target animal safety section', the sponsor submits data on margin of safety study in the target species, tolerability study, reproductive safety study, animal class safety study and other required studies depending on the drug type.

'Effectiveness section' includes data of dose characterization studies/literature and further the field clinical studies, bio-equivalence studies etc.

'Human food safety section' is compulsory for drugs intended for food producing animals only. If the drug product is to be used in a food-producing animal, residues in food products (such as meat, milk, eggs etc.) derived from that animal must be shown to be safe for human consumption. This section includes the toxicology data to determine acceptable daily intake (ADI), residue chemistry data to set tolerance limit and withdrawal time, and microbial food safety data.

For the quality section of the dossier, plans related to 'chemistry, manufacturing and controls (CMC)', for making the drug should be described. It includes data related to details of ingredients and their sources, manufacturing, packaging and storage details, expiry date for test drugs etc.

'Environment assessment (EA) section' is needed under the National Environmental Policy Act (NEPA), wherein the sponsor needs to generate data related to impact of test drug on environment upon its approval. This section describes how much drug is expected to get into the environment and its potential effects on the environment. Specifically applicable for herd/flock treatments, for individual animal treatment e.g. during treatment of pets i.e. dogs and cats, where chances of the drug entering into the environment are rare, the sponsor can apply for waiver off for conducting EA through categorical exclusion application, which indicates that the drug is unlikely to cause a significant environmental impact.

Minor sections i.e. 'product labelling' encompasses labelling information details for immediate container, package insert, outer packaging, shipping label and client information sheet whereas 'all other information section' includes published scientific literature, foreign experience of test drug, medical experience in people and also studies that were conducted by the drug sponsor but not included in the five major technical sections.

During phased application process, once each section is complete, the sponsor submits data to the CVM for review. CVM ensures that the requirements have been met for a particular section, and issues a "technical section complete" letter. CVM also publishes the Freedom of Information (FOI) Summary, which comprises a summary of the safety and effectiveness studies used to support the CVM's decision of animal drug approval. Upon completion of all the technical sections, the sponsor applies for administrative new animal drug application (NADA). The sponsor submits the copies of the technical section complete letters, detailed information on product labeling, and a completed FDA Form 356V (required only for paper based submissions) for an administrative NADA review. Alternatively, the sponsor may submit a single application.

After receipt of all the information, CVM prepares an approval package for the Center Director's signature. If all requirements have been met, the new animal drug application gets approved. An approved NADA means that the drug is safe and effective for its intended use, and that the methods, facilities, and controls used for the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity. New animal drug approvals are announced by a Federal Register notice and added to the Code of Federal Regulations and the Green Book.

### Guidance Documents

CVM Guidance for Industry provides detailed guidelines for planning, conducting and reporting studies with new animal drugs [6]. Moreover, US being the member of International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH); guidance documents issued by VICH are also primarily used during the development of

animal drug candidates [7]. Additionally, applicable human drug guidance from FDA and ICH can also be referred.

## Fees

To support FDA CVM's review process for certain animal drugs, the sponsor pays processing fees under the ADUFA (Animal Drug User Fee Act) legislation [8]. The US FDA announces rates and payment procedures for animal drug application review process in the Federal Register for the particular fiscal year.

## Conclusion

For the animal health industry, the high cost of drug development and manufacturing and relatively lower returns for certain segments make bringing new drugs to market very challenging.

With the, evolving regulations in the drug development processes, heavy market competition, and rising economic volatility, it is imperative to accelerate the drug approval process and to bring new safe and effective drugs early into the market.

US FDA has established stringent rules and regulations for animal drug approval to ensure animal health and welfare; protect public health as well as environmental safety. The animal drug approval processes in the US are quite sponsor friendly allowing for a phased or complete submission of the data. The US FDA guidelines are evolving and it is important to have thorough understanding of new regulations, policies, and updated rules for timely registration of products.

The drug sponsor needs to have a detailed regulatory strategy and forward planning, better understanding of regulatory requirements, and experienced resources. However this can demand increased efforts and lot of costs to get the drug into market. The sponsors have opportunity to discuss each study with the regulators before its conduct and then the results, thus ensuring right data gets generated for smooth registration of products. It is important to understand the entire ecosystem for the animal and the people directly or indirectly affected from the animals. Hence it is necessary to identify the regulatory requirements before performing any strategic planning for the conduct of studies. There is lot of variability in regulatory requirements for various species. It is important that the trials are carefully planned and executed to generate requisite data. Besides this well written documents with focused discussions around Safety, Efficacy, Quality and Environmental Safety may help to accelerate the product registration.

To overcome the hurdles of drug development process and new product registration to comply with FDA standards, partnering with a strong strategic partner with expertise could be an intelligent option for animal health industry sponsors.

A **strategic** outsourcing partner, offering complete assistance through provision of variety of services under one umbrella, right from project management to clinical data management, biostatistics, medical writing and communications, regulatory affairs, and pharmacovigilance, can prove to be a right and flexible option for partnership to any biopharmaceutical company. A service provider with a wide customer base, huge turnover, years of experience, diversified services portfolio, rich pool of resources, and proposing realistic costs can serve as a valuable tool to empower the biopharmaceutical companies to achieve their goals and help them stay ahead of competition and that to in far more cost effective way.



## Acknowledgments

The authors thank Dr. Rajesh Pandey, Offering Lead and Domain Consultant, Medical Writing, Tata Consultancy Services, Mumbai for critically reviewing this manuscript and providing inputs for this article.

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## Conflict of Interest

The Authors declare that there is no conflict of interest.

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