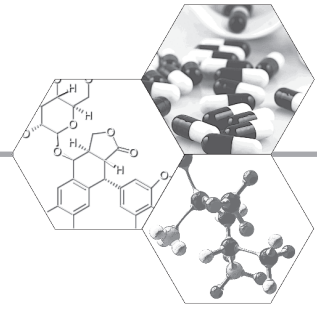

Overview of the animal health drug development and registration process: an industry perspective

Products for animal health commercialization follow a structured progression from initial concept through to regulatory approval. Typically, products are developed for use in either food animals or companion animals. These can be for the intention of disease intervention, productivity enhancement or improvement in a quality of life capacity. The animal health industry is a regulated industry, meaning that a government agency is responsible for oversight of products, both pre- and post-approval. There are three primary US government agencies that ensure quality, safety and effectiveness for the approval of new products and post-marketing compliance.

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This article provides an animal health industry perspective of the veterinary drug-development and approval process. It is not intended to be a comprehensive, in-depth regulatory resource but rather will provide the reader with a general overview of the industry and the drug-commercialization process. Similar to the human pharmaceutical industry, innovation is essential to the existence of mainline animal health companies. It may take 5–15 years and, perhaps, more than US$100 million to advance an animal health drug from initial concept to market. The company has a minimum of 17 years from the time a patent is issued to recoup its development costs, therefore, the urgency required to move a candidate through the pipeline is obvious. The company may be able to extend that patent time by patenting novel formulations, uses or production processes.

This requires new chemical entities to be acquired, discovered or modified from existing products. Drug sponsors typically separate the various stages or phases of work as a means of indicating the various objectives that must be achieved in order to advance the candidate molecule. Preliminary **development phase** work is carried out to characterize the molecule and, if the candidate advances, more extensive and costly **registration phase** studies are then conducted. All animal health drugs (excluding medical devices) are required to be approved by an appropriate regulatory agency prior to marketing. The goal is to ensure quality, safety and effectiveness. An understanding of the US animal health industry product commercialization process, as it intersects with the US FDA Center for Veterinary Medicine (CVM) regulatory **veterinary drug-approval** process, will be valuable to scientists who may wish to contribute their expertise to studies performed within this often-overlooked sector.

Product categories & regulatory agencies

Vaccines and similar biological products that modulate the immune response are licensed by the US Department of Agriculture [101]. The Environmental Protection Agency has authority to register pesticides; however registrations are also required by each state [102]. By definition, these are agents that kill insects or pests, are intended for external application and do not require absorption to achieve efficacy.

The FDA CVM "has authority to approve animal drugs in the USA" [103]. Animal drugs are administered at a specific dose or range of doses, with a specific product label that clearly lists the indication of use along with any precautions, contraindications, warnings and common adverse events.

Animal health business sector

All nonhuman species are encompassed within the animal health business sector; however, two major categories are usually considered: food and companion animals. Food animals are those species that are either intended for consumption as food or that produce products (e.g., milk, eggs) intended for consumption by humans. Companion animals are pets and include dogs, cats and horses. For regulatory purposes, the CVM divides animal species into two additional

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Key Terms

Development phase: Phase of the process where studies are conducted to determine whether a new chemical entity can be registered.

Registration phase: Pivotal studies to support the approval of a new chemical entity are conducted and submitted to the regulatory authority.

Veterinary drug approval: Process by which a new chemical entity is approved by a regional regulatory authority.

categories: major and minor species. Major species are cattle (both beef and dairy), swine, turkeys, chickens, horses, dogs and cats. Minor species are all other species, such as veal calves, sheep, goats, aquaculture species, other poultry, bees and rabbits, for example. To provide perspective, **Box 1** provides recent animal populations compared with humans in the USA.

Most of the animal health companies are business units of a human pharmaceutical parent company. As such, they have the advantage of leveraging the expertise, global scope and support services that smaller, independent companies do not. However, they are often subject to the mergers or acquisitions of the human parent company. Consequently, there has been a net consolidation of the animal health industry [1,2].

The animal health industry is represented by an international trade organization, the International Federation for Animal Health, which provides general information on the scope of the sector [104]. In the USA, the Animal Health Institute provides information on member companies [105]. The animal health market is worth approximately US$20.1 billion worldwide [106]. Approximately 60% of the market is in the USA and the EU. Products targeted at livestock and companion animals account for $11.7B (58%) and $8.4B (42%) of the worldwide veterinary pharmaceutical sales in 2010, respectively [107].

Irrespective to the size of the company, in order to stay competitive, new compounds must continually advance through the development pipeline to enter the marketplace. While generic manufacturing companies may achieve a share of business once a pioneer product loses patent protection, the market rewards innovation to a greater extent.

Box 1. Animal and human populations in the USA.

- 310 million people
- 9.3 billion broiler chickens (slaughter)
- 257 million turkeys (slaughter)
- 110 million pigs (slaughter)
- 34 million cattle (slaughter)
- 3.4 million sheep and goats (slaughter)
- 9 million dairy cows (production)
- 82 million cats
- 72 million dogs

Data from [110,111].

Discovery, development & registration process

Although each company has its own internal organizational structure and approach to commercialization, in general there are three distinct research phases. The initial phase is the discovery phase, when a novel entity is identified; next is the development phase, when additional information is generated to decide whether the drug should proceed to the registration phase, which is when studies are conducted to satisfy the quality, safety and effectiveness approval criteria of regulatory agencies **(Figure 1)** [2].

■ Discovery phase

The company will first conduct a marketing assessment to identify unmet animal health needs that can be addressed and that will result in a satisfactory return on investment. This assessment will guide scientists seeking novel chemistry, new antigens or other innovative technology [3]. The chemistry laboratory synthesizes a variety of similar molecules or analogs, or may provide fermentation-derived materials, which are evaluated by screening against key targets of interest. This process determines structure–activity relationships, in order to find a lead candidate. Sometimes, preliminary adsorption, distribution, metabolism, excretion (ADME) studies may also be used. Typically, the 'checklist' for innovation will include considerations for intellectual property (i.e., patentability), ease of manufacture, initial proof-of-concept studies *in vitro* and *in vivo*, active pharmaceutical ingredient (API) stability, animal safety and preliminary toxicology studies. The discovery and preclinical studies are not typically conducted under good laboratory practice (GLP) requirements.

■ Development phase

Should a company choose to pursue the novel chemistry or technology on the basis of the initial evaluations, additional studies are conducted to further characterize the behavior of the drug substance. Preliminary evaluations regarding where and how to manufacture the potential product are performed. Additional information on the market assessment and other business considerations are also gathered. An internal business decision to advance the candidate to the more expensive registration phase studies may be made. The drug sponsor will contact the CVM and open an investigational new animal drug file, which officially begins the drug-approval process.

■ Registration phase

This phase begins when studies, which have generally been agreed upon by the CVM, are conducted under good clinical practice, GLP or good manufacturing practice (GMP) requirements. All data collected during these studies are used for the purpose of gathering information to fulfill the requirements of the new animal drug application (NADA). These studies, with the notable exception of the total residue study, require a GMP API material. It goes without saying that robust, validated analytical and bioanalytical methods are essential to support these studies. From this point onwards, most protocols for registration phase studies are typically submitted to CVM for concurrence. This is not a requirement for submission, but it helps to avoid any surprises due to changing regulations, changes in reviewers or simple misunderstandings. Concurrence by the CVM does not guarantee that the data generated from a concurred protocol will support the safety or effectiveness of the tested compound.

Toxicology studies, which follow CVM and Veterinary International Conference on Harmonization guidelines, include target animal safety, genetic toxicity studies, 90-day chronic rodent studies, 90-day chronic nonrodent studies, two-generation reproduction studies in rats and a teratology study. Pilot studies and results of the preliminary total residue study are often used to assist in designing the final toxicology studies that are submitted. The toxicology work may require 2–5 years to complete. It should be pointed out that one of the major differences between developing a drug for food animals and a drug for companion animals is that while safety data are required in the target species for both food animals and companion animals, only data in a rodent species, a nonrodent toxicology species and the target species are required to support human food safety requirements in food animal submissions [4].

The NADA is the package of data submitted to CVM for their review and approval. Sections in the NADA are: effectiveness; target animal safety; chemistry, manufacturing and control; environmental assessment; human food safety (food animals only); freedom of information summary; labelling; and all other information. If a sponsor wished to do so, they could submit all the information related to their drug in the NADA. However, the FDA/CVM also has provisions for the submission of a veterinary master file (VMF). This is equivalent to a human health drug master file. VMFs are intended to maintain the confidentiality of the manufacturing information for the API, the compound that provides pharmacological activity. Therefore, one may refer to a VMF in the chemistry, manufacturing and control section of the NADA.

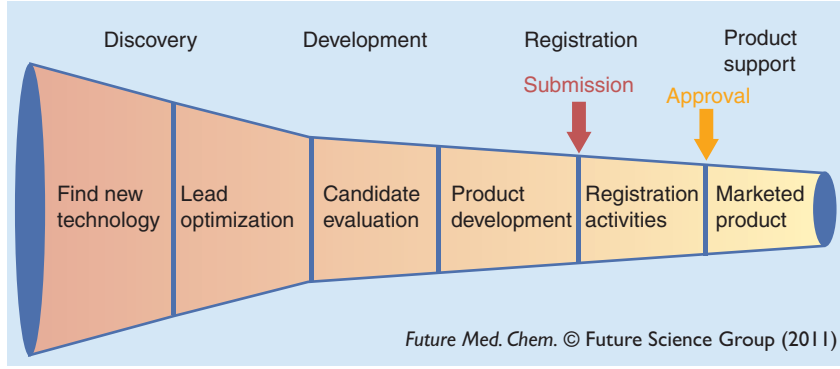

Figure 1. Pipeline stages for animal health drug commercialization. The width of the pipeline reflects the number of compounds in a given phase of the pipeline. Successful advancement of a candidate can take 5–15 years.

Alternatively, each section may be submitted on a 'phased-review' or 'upon-completion' basis, in order to expedite the review and approval process. Typically, the final technical section submitted is the 'all other information' section. When all technical sections are complete under the 'phased-review' process, the company will file an administrative NADA, which is the final step. All an administrative NADA includes is a copy of the technical section complete letters for each technical section, copies of the final agreed-upon labeling, and a copy of the completed freedom of information.

At this time, Animal Drug User Fee Act animal drug application fees are paid; then the FDA completes its review and renders a decision. Once this is finalized, the FDA issues an approval. The final approval is published first as a Federal Register Notice and then published in the Code of Federal Regulations, which is the official record.

At approximately this time, a sponsor typically considers the type of post-approval studies and data that may be conducted for new label claims, such as marketing support data and new formulations, for example. These studies can be important in light of the passage of Animal Medicinal Drug Use Clarification Act, and may provide clarity to an attending veterinarian should they wish to consider extra-label use of an approved drug [108]. The studies cannot, and should not, be used for marketing purposes, however, because they fall outside of the approved label.

Following a food animal drug approval, two reports must be sent to the FDA/CVM. The first is the drug experience report, which includes information relating to the marketing of the drug product, including the quantity sold in the year, all current advertising and promotional materials, the approved label, updates on adverse events from the sponsor's pharmacovigilance program and any new information related to the use of the drug. It is sent to the CVM every 6 months during the first 2 years following the initial approval and then annually thereafter. The other report is the minor changes and stability report (also known as the annual report). As the name implies, this report includes information regarding minor changes in the manufacturing and control information in the approved application, as well as the results of ongoing stability studies on the drug product and API. Both reports are due annually no later than 60 days following the approval date of the registration.

An example of the process

It may be instructive to describe how a product is developed and approved, using the example of bovine respiratory disease (BRD). The possible indication would be as follows: product Z is indicated for the treatment of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida* and/or *Histophilus somni*. In the USA, approximately 5% of the total cattle population acquires BRD each year [5]. When the animals experience stress due to transportation, weather extremes or crowding, the immune system is weakened, allowing the typical causative agents *Mannheimia haemolytica*, *Pasteurella multocida* and/or *Histophilus somni* to cause BRD [6]. Examples of currently approved compounds in the USA that are used to treat BRD are oxytetracycline, ceftiofur, tilmicosin, florfenicol, enrofloxacin, tulathromycin and danofloxacin. These products are administered via subcutaneous injection so as to reduce the potential for tissue damage in the carcass when compared with an intramuscular injection [7]. This illustrates that against the background of a highly competitive commercial situation, the initial marketing assessment must identify unmet needs or improvements that will be valued by the veterinarians and beef producers who will use the new product.

An active discovery process would be required to identify antimicrobial agents that demonstrate acceptable activity directed against BRD pathogens that are desired to be an indication on the drug label. The process allows compounds to be rapidly tested and is very similar to the process used in human health [3,8]. Typically 50% of compounds are 'hits' in this assay and they will then be tested in a bovine model of induced respiratory disease to further screen for efficacy. Of the compounds tested, approximately 20% usually give favorable outcomes and do not result in acute target animal toxicity. This is likely to be the first time the compound is administered to the target animal species, much sooner than when the same event occurs in human drug development. The final test to advance a candidate would be a 'truck and shoot' study, which mimics the transportation of cattle from a sale barn to a feed yard and injectable antibiotic treatment upon arrival. Such studies are expensive because regulations require that all animals treated with the experimental compound be destroyed to ensure that they do not enter the food chain. This is typically reserved for only the most advanced candidates to prove readiness for development studies.

Meanwhile additional basic information is generated on the ADME features of the API. This would be obtained through intravenous and subcutaneous pharmacokinetic studies using a physiological buffered saline or other simple formulation to provide data. This can also allow for assay development of plasma and tissue bioanalytical methods. Even though these studies do not generate pharmacokinetic data for the final formulation, the data may provide useful information for developing the final formulation. During this time, work should begin on a preliminary total residue study. This would use a [^{14}C]-labeled compound administered to two animals at two-to-three time points post-administration. Preliminary target animal safety studies may also begin at this time, in order to verify that the compound was acutely safe to the intended target species.

In parallel to all the data being gathered to support safety and effectiveness, work also commences on manufacturing the product. This may include facilities and inspections, sourcing of key chemical components and packaging and related activities. Toxicology studies, similar to those described above, are performed for the BRD compound.

Once sufficient data on the BRD candidate are collected in the development, the registration phase can begin. The formulation will be finalized during this period. Final toxicology

studies will begin at a later time. A total residue study will be designed and completed. Marketing may begin to consider other species and/or label claims. An investigated new animal drug with a slaughter authorization is necessary before studies can begin. The slaughter authorization is set by CVM for a relatively long withdrawal time for the BRD API, in order to avoid unsafe residues in the meat or other tissues from the animals that go to slaughter. This allows the effectiveness studies to progress without the need to euthanize the large numbers of animals used in the clinical program.

With a slaughter authorization, clinical studies are conducted according to GLP and good clinical practice regulations [9,10]. The slaughter authorization allows the animals to enter the food chain after completing a withdrawal period. The final product formulation used at this point will be manufactured under GMP regulations.

The total residue study should be complete and reported at this time and the results used to conduct a marker residue study. The marker residue study, along with the total residue study, provides data for the determination of the withdrawal time in food producing animals. Assay validation for the marker residue in the target tissue should have been completed prior to the start of the marker residue study. Once completed, the assay is submitted to the CVM for a desk review. A desk review takes place when a CVM reviewer evaluates the written method to determine whether it is appropriate and adequately validated (often a video or live demonstration is provided to the CVM). Once the desk review is completed and passed, the company provides incurred tissue samples to the CVM for distribution to three laboratories for confirmatory validation of the method [11].

The final studies to be conducted are those that are required for the label of the particular compound. These studies could be injection-site toleration, such as microbiological issues around human food safety, for example. The NADA submission of partial or complete technical sections, often in a staged manner, would now commence.

Future perspective

With the One Health Initiative there may be more interaction between the regulations for animal products and human-use products [109]. For example, zoonotic disease agents may be of interest to both physicians and veterinarians, with treatment modalities and experiences that can be transferred to ensure the best possible outcome. It is conceivable that these interactions might extend to regulatory agencies as they consider how best to use anti-infective agents in animals to prevent disease in humans.

Novel modalities, such as nanotechnology and immunomodulatory compounds, for example, may require new guidance to be developed. Indeed, the CVM currently has an innovation exploration team beginning to dialog with the industry to address these future needs. It is foreseeable that some of the registration phase studies required in the USA may be further harmonized with those required in other regions or perhaps a master dossier might become a possibility, in order to streamline the process.

Executive summary

Animal health business sector

- This section contains a review of the types of markets and products that comprise the animal health pharmaceutical business.

Research & development process

- Each company is internally organized differently; the goal is to advance a drug candidate through the process, usually beginning with a product concept and ending with completion of studies to support a regulatory review. This is illustrated by the example of how a candidate molecule proceeds through the numerous studies needed to demonstrate quality, safety and effectiveness with the goal of a regulatory approval for the treatment or control of bovine respiratory disease.

Regulatory approval process

- A description of the US FDA Center for Veterinary Medicine submission components included in a new animal drug application data package is provided.

Future perspective

- With the One Health Initiative, there may be more overlap between animal products and human-use products targeted to infectious disease.
- It is foreseeable that some of studies required for the approval of a new animal drug in the USA may be further harmonized with those required in other regions. New regulations will be necessary to address the new interventions that currently do not fit within the existing paradigm.

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