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Changing innovation into a registered product: From concept to regulatory approval

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ABSTRACT

Innovation in animal health pharmaceuticals is important to address unmet and underserved medical needs, and often comes from products initially developed for human medicine. The purpose of the review is to help readers understand how breakthroughs from human biotechnology may be developed for use in veterinary medicine, while understanding the key drivers to success, the difficulties of regulatory approval, and the realistic risks and rewards of developing applications for animals. The types of human drugs which may be useful for veterinary applications are reviewed, including examples. The regulatory path is discussed, with a review of the various oversight agencies, and the categories of data required to be submitted, including safety, efficacy, manufacturing, environmental impact and human food safety. In conclusion, the cost, development time, and barriers to innovation in veterinary medical pharmaceuticals are discussed.

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1. Introduction

In the last few decades, there has been an explosion of innovation in human biomedical science, as insights from basic biology have been translated to advances in clinical medicine. Most of this innovation did not have a similar significant impact on veterinary clinical medicine, until the last few years, which have been marked by some progress in bringing scientific breakthroughs to animal health. This review article will discuss some of the reasons for this shift, outline some of the opportunities and barriers for innovation in animal health, and give examples of recent innovative products that have come to market (see Table 1). Finally, a summary of key steps needed to successfully translate biomedical innovations through regulatory approval to marketed products will be outlined.

2. What is innovation?

Innovative approaches and products can be defined as those that provide a solution to an unmet medical need, where there is currently no product available for treatment, diagnosis or management of a disease. In addition, there may be innovative solutions to underserved medical needs; for example, when current treatment options may be available, but either have higher than acceptable risks for some patients, or have marginal efficacy. For example, carprofen and other drugs that inhibit the cyclooxygenase enzymes are commonly used for the treatment of pain and inflammation associated with osteoarthritis (OA) in dogs, and although efficacious, may cause severe effects in some dogs [1]. For the purposes of this review, incremental improvements, such as a new formulation for a marketed drug, or another drug in a similar class, are not considered true innovations. For example, new chemical entities (NCEs) that work through a new mechanism of action, thereby providing an improved safety and/or effectiveness profile, are considered innovative, such as grapiprant, a recently approved drug for treatment of pain and inflammation of OA in dogs. Grapiprant is a prostaglandin EP4 receptor antagonist, with the unique mechanism of action of preventing prostaglandin E2 from binding the EP4 receptor, thereby inhibiting pain and inflammation without inhibiting the formation of other prostanoids [2]. For vaccine technologies, innovations include breakthroughs in vaccine adjuvant technology that might overcome low response rates, such as the anti-gonadotrophin releasing hormone vaccine developed as an alternative to castration of pigs [3].

Other examples of innovation include completely new approaches to therapy, such as cell based treatments used for regenerative medicine [4], or gene therapy, the delivery of a therapeutic protein by treatment with a viral vector carrying the DNA coding for the protein. In veterinary medicine, gene therapy has been pioneered to treat congenital hemophilia in dogs [5].

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Table 1
Innovative drugs, monoclonal antibodies, proteins, and DNA products approved from 2015 to 2016.

Drug	Species	Class	Year of Approval, Agency	Indication
Dexmedetomidine	Dog	NCE[a]	2015, FDA 2016, EMA	Noise Aversion
Pegbovigrastim	Cattle	Protein	2015, FDA	Mastitis prevention
Grapiprant	Dog	NCE	2016, FDA	Pain and inflammation from osteoarthritis
Capromorelin	Dog	NCE	2016, FDA	Appetite stimulation
Bupivicaine liposomal injection	Dog	NCE	2016, FDA	Long acting local anesthesia
Rabacfosadine[b]	Dog	NCE	2016, FDA	Lymphoma
Blontuvetmab	Dog	Mab[c]	2015, USDA	Lymphoma
Tamtuvetmab	Dog	Mab	2015, USDA	Lymphoma
Bacterial produced plasmid DNA/liposome carrier	Cattle	DNA	2015, USDA	Bovine respiratory disease
Interleukin-2 immunomodulator	Cat	Protein	2015,USDA	Sarcoma
Anti-interleukin-31	Dog	Mab	2015, USDA	Allergy
DNA vaccine	Dog	DNA	2015, USDA	Lymphoma
Torasemide	Dog	NCE	2015, EMA	Diuretic
Desoxycortone	Dog	NCE	2015, EMA	Addison's disease

[a] New chemical entity.
[b] Conditional approval.
[c] Monoclonal antibody.

Most innovation has traditionally come to veterinary medicine through basic research and development done in the human pharmaceutical and biotechnology industry, where, for example, large scale screening of chemical libraries against novel targets can be performed. More recently, early stage companies have become aware of the possibilities of using their compounds and technologies for animal health applications, but due to a lack of understanding of similarities and differences between the animal health and human health worlds, companies have had difficulty in understanding and exploiting the potential of veterinary applications.

In order to successfully bridge from human to veterinary applications, it is important to understand species differences. Drugs that are proteins, rather than chemicals, in general, are species specific. For example, recombinant human erythropoietin, although used in some limited ways in dogs and cats with anemia, can cause animals to mount an anti-erythropoietin immune response, thereby potentially worsening anemia [6], and no feline or canine erythropoietin product is yet available. Similarly, the bovine version of recombinant growth hormone was developed to increase milk production in cattle [7]. An example of an exception to this rule is the decapeptide GnRH agonist drugs such as deslorelin (Suprelorin™) which are for the most part, equally effective in all mammalian species, because of the conservation of the sequence of GnRH and GnRH receptors across species.

Many innovative drugs in human health are monoclonal antibodies such as trastuzumab (Herceptin™) that targets a protein called Her2 for treatment of breast cancer [8] and adalimumab (Humira™) that targets tumor necrosis factor-alpha, for treatment of rheumatoid arthritis and other inflammatory conditions [9]. These antibodies have been "humanized" – that is, their basic structure has been modified, most commonly from mouse antibodies, to resemble more closely human antibodies. These drugs do not have applications in animal health, because, like protein drugs, it is expected that animal's immune systems recognize them as foreign and mount an immune response. However, if a human monoclonal antibody treatment has proved effective in a therapeutic application where the underlying mechanism of action is similar in animals and humans, i.e. the target has been validated, it has now been shown to be possible to "caninize" or "felinize" monoclonal antibodies to then use in dogs or cats [10]. In this way, human medicine first may validate the target which then makes the development of a similar therapeutic for animals promising.

Similarly, stem cells and gene therapies can be developed that are informed by their human health equivalents, but must be species specific products in order to be effective and safe in veterinary medicine.

Companies with interesting new human drugs or therapies can use data they have generated in rodents and dogs as part of their human health development program to help predict if their product could work in animals. For example, for most human drugs safety testing in dogs is required, so there is often useful dog safety data available that can help move a veterinary application forward. A less appreciated but crucial component of developing a new drug is figuring out the chemistry and manufacturing issues, and if that work is being done for human drug development, companies can use that information to advance veterinary applications as well.

3. Regulatory pathways

Regulatory approval of drugs and therapeutics for animals takes various paths depending on the mode of action of the therapy as well as the country in which approval is sought. The scope of this article cannot serve as a detailed guide for regulatory approval of specific products, but is intended to give an overview of the regulatory processes and highlight important issues.

Regulatory requirements world-wide fall into the following categories:

- Effectiveness
- Target Animal Safety
- Human safety
- Environmental impact
- Human food safety
- Manufacturing (also called chemistry, manufacturing and controls or CMC)

The last category, human food safety, applies only to products which are intended to be used in food animals, where there may be concerns about drug residues in meat, milk or eggs. The Sponsor (the company developing the drug) must show that the residues of the drug that might remain in food intended for humans are safe, and define the withdrawal time (i.e. the length of time from use of the drug until animal food product can be consumed by humans) based on when this safe level might be achieved. In Europe, the registration dossier to be provided to European Medicines Agency (EMA) groups the data into three main sections: 1) manufacturing,

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