Pharmaceutical challenges in veterinary product development

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Abstract

There are many similarities between the human health and animal health industries. Both industries are research driven, have global presence, are highly regulated, and have to profit in a competitive business environment. However, there are also notable differences. This review highlights and discusses those differences as they relate to the pharmaceutical challenges in veterinary product development. This paper provides a brief review of the animal health pharmaceutical product landscape, segmentation, and market evolution; highlights challenges and special considerations in veterinary drug delivery; and identifies unmet needs in animal health along with recent advances.
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Keywords: Veterinary drug delivery; Controlled release; Modified release; Large animals; Small animals

Contents

1. Introduction

Drug delivery technology has played an important role in the development of the animal health pharmaceutical industry [1–3]. Correspondingly, the animal health pharmaceutical industry has been a pioneer in the application of drug delivery technology, engineering and biotechnology to product development. The need for new drug delivery technology for animal health is driven by five major factors:

- To enhance consumer convenience and compliance
- To improve the pharmacokinetics of drugs
- To extend patent life of proprietary molecules
- To provide product differentiation

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• To assure target animal and consumer safety

There are many similarities between the human health and animal health industries. Both industries are research driven, have global presence, are highly regulated, and have to profit in a competitive business environment. However, there are also notable differences. Special considerations in veterinary product development are cost sensitivity, weather sensitivity, multiple species and breeds, variability in animal weights, consumer compliance and convenience, user and target animal safety, and husbandry practices [4,5].

In developing human health products, drug safety and efficacy evaluation is a slow process consisting of pre-clinical studies in animal models followed by Phase I studies to evaluate safety and Phase II and III to confirm safety and efficacy. In contrast, the clinical testing of veterinary product is facilitated by the ability to rapidly establish safety and efficacy in target species, circumventing the need for pre-clinical and Phase I evaluations. The time from bench to market may be 2–3 years shorter for animal health drugs compared to human medicinals depending on the therapeutic class, duration of therapy and the target species. However, veterinary formulations are typically more complex and more diverse. It is seldom recognized that the formulation development challenges for animal heath products are equivalent to and often exceed those for human pharmaceuticals. Hence, formulation development costs for an animal health product comprise a larger proportion of the overall development cost than do human pharmaceuticals.

While animals are often used to test and model drug safety, pharmacokinetics and efficacy in humans, experience teaches us that drug molecules and dosage forms often have to be species tailored for veterinary application. In the livestock sector, the formulation challenge is to develop dosage forms that minimize the time and cost associated with the mass treatment of herds with the focus on animal welfare, ease of administration, season-long protection and human safety. Injections, feed additives, ruminal boluses, and topical pour-ons are commonly used for drug administration to livestock. Formulation and drug delivery considerations for companion animals are dictated by a different set of circum-

stances, such as the ease of use to the pet-owner, pet–owner bonding, pet compliance, and dosing flexibility. Medicated collars, sprays, powders, shampoos, spot-ons and palatable tablets are commonly used for companion animals.

The objectives of this presentation are to: (i) briefly review the animal health pharmaceutical product landscape, segmentation, and market evolution; (ii) highlight the veterinary drug delivery challenges and special considerations; and (iii) identify unmet needs in animal health along with recent advances. This review will not cover vaccines except to compare and contrast key formulation issues versus pharmaceuticals.

2. Animal health pharmaceutical landscape

Based on a recent survey by Wood Mackenzie Global Consultants [6], the worldwide animal health market was estimated at $11 billion in sales in 1998. North America and Western Europe account for ∼ 60% of the worldwide animal health pharmaceutical market (Fig. 1). Anti-infective pharmaceuticals and parasiticides are the major therapeutic segments comprising 50% of the market (Fig. 2).

Livestock products dominate the animal health pharmaceutical market and account for 70% of the sales (Fig. 3). However, it is interesting to note that the sales of livestock pharmaceuticals remained essentially flat over a 6-year period from 1993 to 1999 but the companion animal product sales increased by almost 100% during this period (Fig. 4).

Historically, oral medications and injectables have been the primary veterinary dosage forms in animal
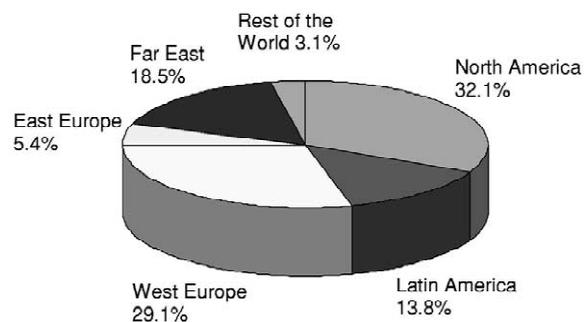

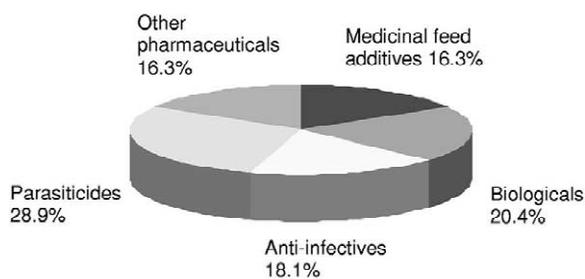Fig. 1. Worldwide animal health market by region.

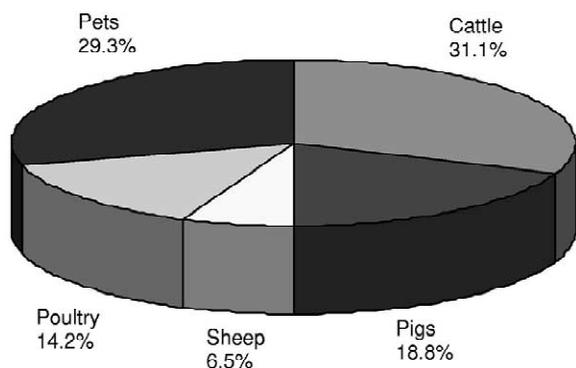Fig. 2. Animal health sales by therapeutic segments.

Fig. 3. Comparison of livestock (cattle, pig, sheep, and poultry) and companion animal markets by market share.
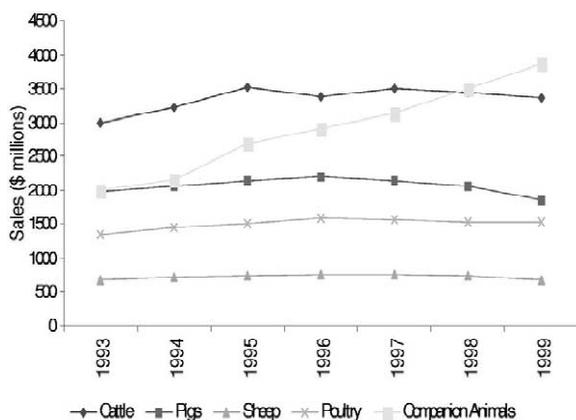

Fig. 4. Change in sales from 1993 to 1999 for livestock and companion animals.

health. However, the trend towards companion animal pharmaceutical products has resulted in the launch of several convenient dosage forms, such as pour-on, spot-on and palatable tablets as illustrated in Table 1.

Table 1
Recent veterinary companion animal products

Product	Formulation
Program (lufenuron)	Tablet (dogs)
	Oral suspension (cats)
	Injection (cats)
Frontline (fipronil)	Spray (dogs/cats)
	Spot-on (dogs/cats)
Advantage (imidacloprid)	Spot-on (dogs/cats)
Anipryl (selegiline)	Tablet (dogs)
Clomicalm (clomipramine)	Tablet (dogs)
Enacard (enalapril)	Tablet (dogs)
Gastrogard (omeprazole)	Oral paste (horses)
Revolution (selamectin)	Spot-on (dogs)
Rimadyl (carprofen)	Tablet (dogs)
	Injectable (dogs)
Sentinel (milbemycin)	Tablet (dogs)
Droncit (praziquantel)	Tablet (dogs)
	Injectable (dogs)

The recent shift in focus from livestock to companion animals has been driven particularly by economic, environmental and regulatory factors. As a result, many large pharmaceutical companies have been seeking to leverage their powerful human health portfolios to rapidly introduce new chemical entities (NCEs) into the companion animal sector in common therapeutic areas. Anti-infectives and chronic conditions are two therapeutic areas of opportunity in this regard.

3. Veterinary drug delivery challenges and special considerations

The animal health pharmaceutical industry faces some of the same formulation challenges as human pharmaceutical companies. However, the diversity of species and breeds, the range in body sizes, regional differences, differences in metabolism and biology, seasonal variations, disease states, economics, and other factors complicate drug delivery strategies for veterinary formulations.

Species differences affecting the design and performance of veterinary dosage forms include ADME differences, feeding habits, environment, age and management practices. Species differences in metabolism can affect elimination of drug [7,8]. Baggot [5] showed large differences in the half-life of six drugs

Table 2
Half-life of six drugs measured in cattle, horses, dogs, cats and humans

	Ruminant (hrs)	Horse (hrs)	Dog (hrs)	Cat (hrs)	Human (hrs)
Pentobarbital	0.8	1.5	4.5	4.9	22.3
Amphetamine	0.6	1.4	4.5	6.5	10–15
Salicylate	0.8	1.0	8.6	35	4–8
Sulfadimethoxine	9	11.3	13.2	10.2	40
Trimethoprim	0.8	3.2	3		10.6
Phenylbutazone	43	3–6	2.5–6		72

measured in cattle, horses, dogs, cats and humans (Table 2). The absorption rate of drugs can also vary across species. For example, the absorption rate of kanamycin in horses is six-fold higher than in dogs after intra-muscular injection [9]. Species-related pharmacokinetic and metabolic differences can result in widely different drug exposure levels or bioavailability. Marshall and Palmer [10] demonstrated that the bioavailability of amoxicillin was much higher in cats compared to the pig, dog, calf and horse as shown in Fig. 5. This may be explained, in part, by the idiosyncrasies of drug metabolism in cats [11].

Differences in animal weight that occur both among and within species present another veterinary product development challenge. Table 3 is a comparison of the body weight ranges for various species. Assuming the same mg/kg dose for a new
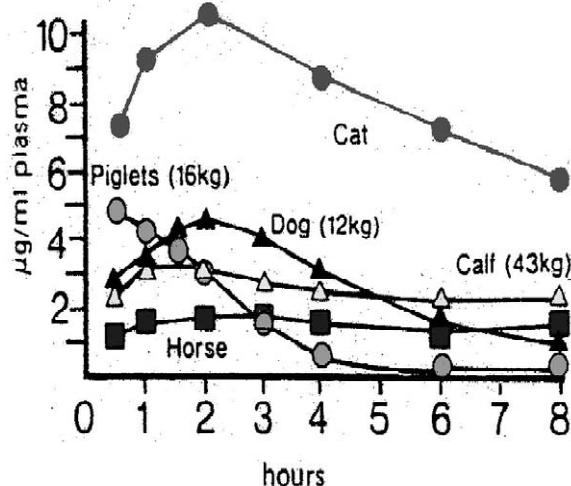

Fig. 5. Bioavailability of amoxicillin in cats compared to pigs, dogs, calves and horses (an example of the idiosyncrasies of drug metabolism in cats).

Table 3
Comparison of the body weight ranges for various species

Species	Weight range (kg)
Cat	1–4
Dog	3–43
Horse	408–433
Cattle (beef)	266–641
Dairy cow	600–700
Sheep	54–66

chemical entity (NCE), the total dose can range over 12-fold within dog breeds, and over 700-fold between small and large animals. The variation in body weight can cause under-dosing or over-dosing, which can be a problem in terms of efficacy and safety for potent drugs.

Companion animal drug delivery needs generally mimic those in human pharmaceuticals with similarities in disease states. Therapy for companion animals is not usually as cost sensitive as for livestock. The therapeutic agents are typically small molecules dosed chronically. Once-a-day oral or topical dosing is the preferred dosing regimen and mode.

Systemic safety and toleration are important considerations, along with owner safety and convenience. In contrast, livestock therapy is usually cost sensitive, and value versus cost ratio is an important consideration. The therapeutic entity is usually small molecules or in some cases large molecules (proteins) dosed acutely or sub-chronically at high doses. The typical duration of treatment ranges from 2 weeks to 6 months. Injections are often the preferred dosage form. Local toleration and injection site residues are major concerns. Tissue residue levels constitute a major consumer safety issue and dictate the meat withdrawal time.

Although many of the formulation issues for companion animals and livestock are similar, the therapeutic and safety implications may be divergent. For example, pain and injection site reaction in companion animals is a pet-owner compliance and acceptance issue, whereas, in livestock, the overriding concern with the injection site is tissue residue and meat withdrawal time. The dosage form options between companion animals and livestock may also vary substantially. Although injections are common and preferred for livestock, oral administration is

preferred for companion animals. Controlled release oral dosage forms for companion animals is challenging because of gastrointestinal physiology and eating habits.

Vaccines fall into a separate category altogether. In the US, vaccines are subject to a separate regulatory approval process and quality standards. The vaccine market is very cost sensitive and vaccines are usually larger molecules administered in low doses. Single shot therapy, which requires no subsequent booster shots, is a high want, albeit an elusive, goal in many cases.

4. Leveraging from human health: opportunities and constraints

As previously noted, there are considerable similarities between veterinary and human health dosage forms and therapeutic indications, particularly with respect to companion animals. Many major pharmaceutical companies have recognized this synergy and have sought to capitalize on this opportunity to either extend the use of human health drugs to animals, or, to use the human health drug candidate as a lead to test proof of concept in a therapeutic class in veterinary medicine.

Although the most common dosage forms for both humans and animals are tablets and injectables, converting human health formulations to animal health formulations may not always be straightforward. Special considerations such as (i) multiple doses, (ii) lower strengths, (iii) dosing on a mg/kg basis for animals versus mg for humans, and (iv) palatability requirements, need to be factored in the design of animal health dosage forms and can add to the complexity of development.

Most tablets designed for humans are designed based on a milligram (mg) dose, on the assumption that an average human weighs ~70 kg. For animals, one needs to consider that multiple strengths are necessary because of differences in the weights of animals and because doses are administered on a mg/kg basis. Hence, typically three to four tablet strengths are developed for more accurate dosing. Additionally, tablets may be scored for dose titration.

Lowering the dose on an existing human health tablet for use in animals is not always straightforward. The easiest approach for lowering the dose would be to manufacture smaller tablets (common blend strategy); however, this approach is not always feasible due to constraints associated with manufacturing very small tablets. Table 4 illustrates the effect of lowering the dose on the stability of two tablets (high dose: human health indication; low dose: animal health indication). The lower dose for the animal health product was achieved by simply reducing the percentage of drug loading in the same formulation used for the human health tablet. Under accelerated stability conditions the low dose tablet (dilute formulation) exhibited greater instability. This is commonly observed in the development of tablets and is believed to be due to more intimate contact of the drug with excipients in low dose tablet formulations. Therefore, one needs to consider stability issues when reformulating higher strength tablets for animal health purposes. A simple reduction in tablet size or reducing drug concentration to achieve the desired tablet strength is not always straightforward. Impurity and degradation product levels must be

Table 4
Stability of a 'concentrated' tablet formulation relative to a 'dilute' tablet formulation

	Initial (%)	Total impurities as per cent of parent drug (%)		
		3 Weeks (40 °C/75% RH)	6 Weeks (40 °C/75% RH)	12 Weeks (40 °C/75% RH)
Human health tablet (higher drug loading)	0.10	0.08	0.20	0.20
Animal health tablet (lower drug loading)	0.10	0.66	1.00	1.70

taken into consideration to demonstrate the quality and safety of the drug product. There is some latitude in terms of impurity levels allowable in drug products for animal health versus established thresholds in human health products, as per current ICH guidelines summarized in Table 5.

Stability issues become more complex when developing 'palatable' oral dosage forms. The simple approach for developing a palatable oral dosage form is to add a yeast-based or a meat-based flavor to the tablet blend. These flavor systems, which typically consist of a number of components, could themselves react with the active agent or affect tablet dissolution. Furthermore, analytical method development becomes a challenge for palatable tablets, since many ingredients are present in the flavor systems.

As mentioned before, the addition of a flavor (i.e. yeast) to the tablet blend is perhaps the simplest approach towards the development of a 'palatable' tablet. However, this approach is only feasible in certain cases and for certain species. In the case of a 'bland' or a 'moderately bitter' drug targeted for dogs, a simple flavor addition would suffice in order to achieve > 80% free choice acceptance. If there is an odor issue with the drug then a simple flavor addition may not be adequate. In the case of human health drugs, formulators are more concerned with the taste of the drug. However, odor may be more important than taste for free choice dosing in animals. Table 6 compares the free choice acceptance in dogs for a bland drug, bitter drug, and an odorous drug. The result shows that an odorous drug is the least attractive to dogs with only a 20% free choice acceptance rate, while a bitter and a bland drug had free choice acceptance rates of 40–60%, respectively. A simple flavor addition to a bitter drug results in > 90% free choice acceptance. In the case of an

Table 6
Free choice acceptance in dogs for a bland drug, a bitter drug and an odorous drug

	Free choice acceptance rates in dogs (%)	
	Plain tablet (no flavor)	Flavored tablet
Bland drug	~ 60	~ 100
Bitter drug	~ 40	~ 90–100
Odorous drug	~ 20	~ 55

odorous drug, a simple flavor addition does not increase palatability to the desired level and one may need to consider other approaches for odor masking. As one could imagine, the issues associated with free choice acceptance, taste, and odor are even more complicated when dealing with felines. The free choice acceptability of conventionally flavored tablets in cats is typically less than 50%. In general, a formulation scientist developing a palatable oral product for companion animals should consider the following: (i) compatibility of active drug with the flavor base; (ii) global acceptability (regulatory approval of meat based flavors in EU will be an issue); (iii) acceptability by dogs and cats; (iv) stability of the flavor; and (v) ease of characterization of the flavor.

Another issue that needs to be considered when developing an animal health oral product is 'food effects'. As in humans, the bioavailability of some drugs can be profoundly affected either negatively or positively by food and water [12,13]. As an example, Watson [14] reported that there were no food effects with tablets; however, food effects were observed with suspensions for chloramphenicol palmitate in cats. This 'dosage form specific' food effect was observed with chloramphenicol in cats as illustrated in Table 7. In the case of oral dosage forms designed for humans, food effect issues can be managed by requiring the patient to take the medication with or without food. In the case of animals, food effects are not as easily managed. Formulators are often asked to minimize food effects through formulation approaches for animal health dosage forms. Requiring the animal to take the medication with or without food or with plenty of water may not be convenient in the field.

In the case of injectable formulations, developing

Table 5
ICH guidelines on impurity levels

	Individual impurities as per cent of parent drug	
	Human health	Animal health
Report	0.1	0.3
Identify	0.5	1.0
Qualify	0.5	1.0

Table 7
'Dosage form specific' food effect with chloramphenicol palmitate in cats on two feeding regimes

Regime	Formulation	AUC (mg/h per l)	Urine chloramphenicol mass (mg)
Fasting	Tablet	204 ± 61	28 ± 5
	Suspension	115 ± 26	16 ± 3
Fed ad libitum	Tablet	199 ± 43	28 ± 10
	Suspension	177 ± 30	26 ± 4 [a]

Dose rate 100 mg per cat. Results are mean$\pm$S.E.M. of five values, except as indicated. There were no differences in systemic availability from tablets when given while fasting, with water while fasting or with food ad libitum. When these data were combined (AUC 224 ± 29, urine drug mass 25 ± 3) and compared with data for the suspension, the AUC and urine chloramphenicol mass for the suspension were significantly reduced in fasted cats ($P < 0.02$ and $P < 0.05$, respectively) but not in fed cats ($P > 0.05$).

[a] Mean$\pm$S.E.M. of four values.

an injectable for animals is more complicated than humans for several reasons. One of the primary reasons is injection site toleration (IST). IST is a common issue for both human health as well as animal health products. However, the IST issue for human health products can be overcome by changing the route of administration (i.e. switching to i.v.), by administering less of the drug at the site (multiple injections), or using more complex formulation technologies to alleviate pain on injection. In the case of animals, especially livestock, there is an economic constraint that limits dosing options. Intravenous administration and multiple injections for animals are not always feasible due to labor cost and management practices. In fact, as more animal health injections are targeting a 'one-shot' therapy, whereby a high drug loading formulation is administered to the animal to minimize multiple injections, the risk of injection site precipitation and injection site toleration concerns are increasing. Local tissue reaction can have a detrimental effect on the extent of drug absorption from injections [15–17]. In companion animals, IST concerns are primarily focused on pain and swelling. In the case of livestock injection site toleration could also have an impact on human food safety and meat quality. All of these factors can be severely detrimental to the commercial success of the product. Therefore, injection site toleration is an important criterion that must be assessed early in the development program as part of the technical feasibility evaluation.

For economic reasons, most injectables developed for animals health are multi-use products. This adds a considerable amount of complexity to the formulation development for the following reasons: (i) the need to select a preservative if the formulation is not self-preserving; the need to demonstrate that the preservative is stable and compatible; (ii) the formulation must pass the preservative efficacy test (PET); meeting the stringent EU PET criteria is often challenging; (iii) the need to select stoppers that can withstand multiple punctures; and (iv) the need to study the in-use stability of the product.

In-use stability can sometimes present intractable problems that require extensive investigations and may limit the utilization time and storage conditions for the product. An example of this is shown in Fig. 6, where a color change caused by trace formation of an oxidative degradant, altered the product appearance although there was no significant impact on stability or impurities [18].

Finally, for cost and convenience reasons, long-acting injectables are preferred in animal health. Typically, long-acting injectables are more complicated to develop and the technology options are limited, particularly under cost constraints. Formulation constraints such as high viscosity often preclude administration with dosing guns making herd treatment difficult for livestock. Refrigeration due to stability constraints may very detrimental for veterinary products. The usefulness of many controlled release technologies is limited by low drug loading. Tissue residue is a major concern for long-acting injectables and can detrimentally impact the meat withdrawal time in livestock products [19]. The residue issue may not be restricted only to the drug but is also relevant to the excipients. These limitations limit the choice of technologies and excipients
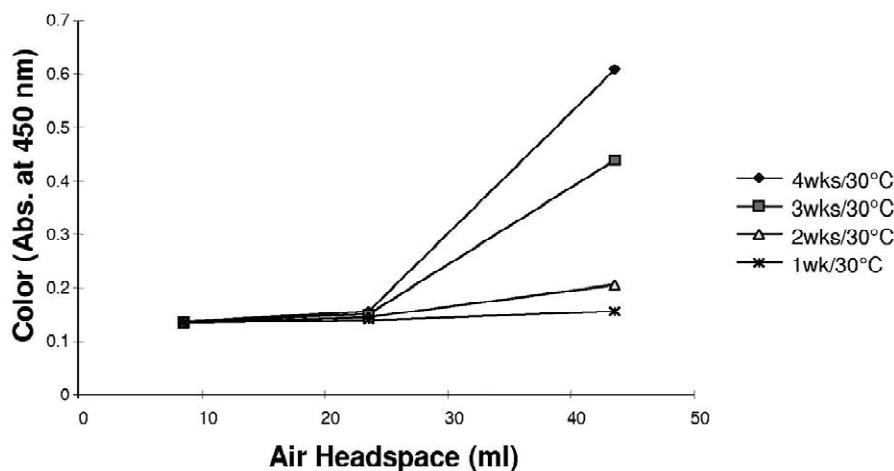
Fig. 6. Color change caused by trace formation of an oxidative degradant which altered the product appearance although there was no significant impact on stability or impurities [18].

that are suitable for use in long-acting veterinary injections.

5. Value optimization through drug delivery systems and formulations

As mentioned earlier, product differentiation is an important means of gaining an edge in a competitive market. Differentiation, through new drug delivery systems, can improve both the performance of new drugs and can help to maximize returns from existing products. Formulation and drug delivery technologies that result in a higher level of efficacy, increased stability, long duration of action, improve patient compliance and enable quicker and easier treatment will subsequently improve commercial performance. Merial's ivermectin is a good example of value optimization through multiple product introductions tailored to species and customer needs. Merial markets injectable, drench, pour-on and bolus versions for use in livestock, a premix product for pigs, paste and liquid formulations for horses, and tablets for use in small animals [20].

Convenience of use and user safety are key considerations when developing products especially for livestock. Examples are sustained release boluses and pour-on formulations. Early bolus products, which typically contained non-eroding metal com-

ponents or metal weighting devices, presented problems for the meat processing industry [21]. This prompted Pfizer to begin the development of a second-generation bolus product. Pfizer launched the Paratect Flex in the late 1980s [22]. At the same time, other companies such as Hoechst Roussel (Vet's Panacur Bolus), Schering-Plough (Autoworm), and Merial (Ivomec SR) were also working on developing a non-metal bolus or metal materials that erode gradually over the delivery period.

Another example of value optimization via formulation technology is pour-on products for delivering anti-parasitics in livestock. Pour-on formulations are liquid solutions that are poured onto the dorsal skin (back) of the animal [23–26]. To be effective as a pour-on, there must be sufficient penetration into the stratum corneum and other layers of the dermis to allow systemic absorption and at the same time prevent removal of the drug by environmental conditions such as rain [27]. Merial's eprinomectin was introduced as a pour-on from the start of its commercial life. Pfizer and Fort Dodge have also added pour-on formulations to their endectocides. The popularity of pour-on products has resulted in several generic introductions of ivermectin pour-ons.

Spot-on formulations are similar in concept to pour-ons but are targeted for companion animals. The main difference between pour-on and spot-on formulations is that the latter are high concentration

and small volume. Recent examples of spot-on formulations include Merial's Frontline (fipronil), Pfizer's Revolution (selamectin) and Bayer's Advantage (imidacloprid). Spot-ons represent an attractive complementary dosage form to the traditional injectable and oral dosage forms.

Injections, tablets, oral solutions and soluble powder still represent the main dosage forms for delivering active ingredients in veterinary medicine. The major drug delivery needs and value opportunities in this area are sustained release injectables, palatable dosage forms for oral administration and devices. Sustained release injectables are critical for livestock [28]. Several injections may be required over the course of treatment; therefore, the development of long-acting formulations has been undertaken by a number of companies. Some examples of long-acting injectables are Nuflor 300 (Schering Plough), Advocin 18% (Pfizer) and Posilac (Monsanto).

Chronic administration of tablets to companion animals is particularly challenging. Although tablets allow for administration of the therapy without the veterinarian, owner or patient compliance can be a problem because the pet may not consume all or part of the tablet. Palatable tablet versions have been developed in order to make administration of tablets easier. Examples include Program (Novartis) and Frontline (Merial).

6. Unmet drug delivery needs in animal health, future trends and concluding thoughts

In a survey of pharmaceutical scientists from both academia and industry at the 1999 American Association of Pharmaceutical Scientists (AAPS) meeting in New Orleans, three major areas of drug delivery needs in animal health were identified, namely:

- Convenient delivery for companion animals
- Long-acting implants and injections
- Dosing devices and needle-free injectors

6.1. Convenient delivery for companion animals

The global companion animal market is an important segment of the animal health market. It has higher profitability, less price sensitivity and a higher growth rate than livestock. Unlike the livestock segment, it is not cyclical. Furthermore, this segment presents opportunities for research synergies and spin-offs from human health with less consumer regulatory pressure than the food animal segment. The most common dog medications are flea/tick (72%), heartworm (66%), and ear medications (30%), while common medications for cats are flea/tick (49%), hair-ball remedy (48%), and ear medication (22%).

Convenience, defined as improvements providing customers with increased pet bonding, ease of dosing and safety, is key to commercial success in this segment. The drug delivery needs are once-a-day or less frequent dosing, palatable products, and ease of dose administration. At present, there is a knowledge gap with regards to fundamental understanding of companion animal physiology and dosage form performance. Some features of the comparative gastrointestinal physiology in dogs, cats and humans are summarized in Table 8. Gastric retention and intestinal transit may vary as a function of species and dosage form, which in turn, may affect the technical feasibility of once-a-day oral dosing with sustained release formulations in dogs and cats. Sutton [29] reported that drug release from matrix tablets in dogs may be highly variable and dependent on gastric emptying time, and that large matrix tablets might be retained in the stomach in dogs. In contrast, drug release in dogs from coated osmotic tablets was less variable but the tendency for dogs to bite and chew may make coated tablets unsuitable for controlled release dosing of some drugs in dogs. The oral controlled release dosage form of choice in companion animals may be microparticulates.

The dosing problem is further exacerbated in cats due to palatability constraints. While flavored tablets

Table 8
General features of GI physiology in dogs, cats and humans

Stomach volume: cats << dogs
Gastric emptying of beads (1.5–5 mm)
Fasted: cats similar to dog
Fed: retained in cats but not in dogs
Gastric retention related to breed size
Small intestinal transit time may be slightly slower in cats
Intestinal permeability: cats > dogs > man

may be suitable for dosing in dogs, the approach may not be appropriate for dosing in cats. Medicated treats, liquids and food admixes are value-added alternate formulation approaches that may emerge as commercial opportunities in the future. The challenge is to reconcile food versus pharmaceutical quality standards with respect to raw materials, manufacturing process, specifications, and stability. Taste masking for bitter and odorous drugs is a challenge in convenient dosing in companion animal as was described previously. Screening methods to identify and alert taste-problems early in development should become an integral part of the candidate selection process for oral veterinary drugs for companion animals. Such methodology is emerging but has not been adapted to any appreciable extent.

Finally, topical spot-on formulations have become increasingly popular as a convenient dosing option for dogs and cats. However, the topical/transdermal delivery potential of drugs is highly molecule physical chemistry dependent; the key requirements being low dose, low molecular weight and high partition coefficient. Furthermore, the pharmacokinetic and pharmacodynamic profile should be favorable for topical dosing. This includes a long half-life, good tissue distribution and flux, and a large therapeutic index [20]. Formulations for spot-ons typically contain cosolvents and spreading agents. An area of opportunity for next generation spot-ons is the enhancement of topical delivery or sustained delivery platforms that enable less frequent dosing.

6.2. Long-acting injections and implants

There is a continuing need for long-acting injections and implants. The desired duration of release may vary from 2 weeks to 2 years. There are two major unmet needs in this area. The first refers to the technology for long-acting delivery of protein pharmaceuticals and vaccines. The possibility of using a prodrug approach to stabilize proteins was recently explored with porcine somatotropin. An orthovanillin prodrug of pSt shown in Fig. 7 was found to prevent aggregation of the native protein and its use was investigated to deliver pSt to pigs over 2 weeks as an injectable implant [30–32].

The second unmet need in long-acting injections and implants refers to formulation technology to minimize tissue residue and local tissue reaction. Many of the commonly used polymers are known to illicit various degrees of tissue reaction, and their clearance rate from the injection site is often slower than the depletion rate of the drug. Although formulation approaches have occasionally been successful
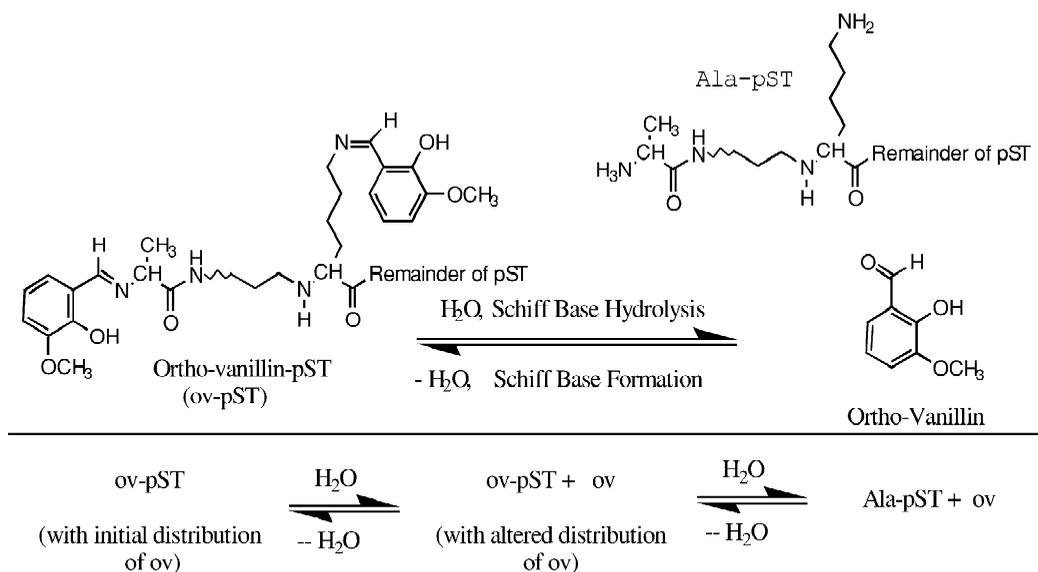

Fig. 7. An orthovanillin prodrug of pSt which was found to prevent aggregation of the native protein.

in improving injection site toleration of irritating drug, the irritation potential is usually molecule or class specific. Depot formulations frequently exacerbate the injection site toleration problems [33,34].

Biodegradability and non-surgical dosing is a requirement for implants in animals. The dosing of herds with implants is particularly challenging and requires specially designed automatic dosing guns. Sterilization of the implant is also a development challenge, particularly for protein pharmaceuticals that are prone to instability. The opportunity in this area is for new polymers and microparticulates that can be injected with a conventional syringe.

6.3. Dosing devices and needle-free injector

'No needles' is a high priority need in animal health, particularly in livestock pharmaceuticals and vaccines, where needles in meat present an unacceptable consumer safety concern. Furthermore, the administration of pharmaceuticals and vaccines using traditional methods is laborious and requires animal restraint. There is risk of injury, stress compromises recovery rates, and normal physiological processes can be altered. Several needle-less injectors have been approved for use in humans or are in development, such as Bioject, Powderject, Mediject, and Westin [20]. These technologies are expensive and are tailored for self-administration of small volume injection of liquids or powders as unit dose. Unfortunately, there is limited relevance of such technologies in animal health. The variations in skin thickness types as a function of species and age render true needle-less administration very difficult. An approach that is under investigation by various companies is a semi needle-less design where short thin needles are located on the tip of each disposable cartridge. The factors to consider in evaluating the technical feasibility and commercial viability of such devices include: regulatory status, contact material, cost, accuracy/repeatability, viscosity range of the dispensing liquid, needle life and cleanability, number of doses dispensed per shot, waste, safety, and ergonomics. It is expected that an animal health version of a needle-less injectable will be commercialized within the next few years.

In conclusion, animal health remains a fertile area for formulation and drug delivery research as evident by the myriad of new dosage forms that are commercialized for veterinary use. There is synergy between human health and animal health in terms of therapeutic area and formulations. Likewise, animal health is value-added to human health in terms of providing animal models and a conduit for prototyping of new drug delivery technologies.

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