Controlled release drug delivery in farmed animals: Commercial challenges and academic opportunities

Michael Rathbone*, School of Pharmacy, Griffith University, Gold Coast Campus, Parklands Drive, Queensland 4222, Australia.

David Brayden, School of Agriculture, Food Science and Veterinary Medicine and UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland.

Abstract

Currently there is a lack of new active pharmaceutical ingredients (APIs) appearing on the veterinary market. In the short term this problem can be offset by developing controlled release drug delivery technologies to extend the commercial life of existing drugs. However, such a commercial opportunity does not come without its challenges. These generally revolve around financial factors, which include limited budgets assigned to conduct veterinary R&D, the cost-competitive amount that can be charged for the finished product and the expensive time-consuming registration process. In addition, the gap between the perceived and actual market needs makes the return on investment hard to defend. It is not surprising therefore that few controlled release products appear on the market for farmed animals, despite their potential advantages to that sector.

The landscape for an academic veterinary pharmaceutical scientist is quite different from that of the industrial one. When you remove the commercial requirement associated with product development, there are numerous fundamental and applied research opportunities, with the outcome of demonstrating the potential worth, or otherwise, of an approach being sufficient to achieve the major goal of academics, publication in peer-reviewed journals. A further opportunity arises when controlled release dosage forms are used as research tools to forward knowledge in the area of animal science.

The aim of this review is to provide a perspective of the current animal health industry through examination of the commercial challenges *per se*, along with the potential for academic collaboration that lie within this demanding area of pharmaceutical science.

Key Words: Controlled release, modified release, veterinary drug delivery, large animals, farmed animals, livestock.

Introduction

Animals can be divided into farmed, companion and wildlife (including exotic and zoo species) [1]. Thus the potential patent population encompasses a diversity of species and breeds; a wide range of body sizes; involves animals living under a large variety of regional differences (e.g., range versus feedlots), exhibiting differences in metabolism, displaying differences in disease states, encompassing a wide range of feeding habits (e.g., cats have quite different feeding habits to dogs) and undergoing a variety of management practices (e.g., water versus feed versus air drug delivery systems for poultry) [2]. Farmed animals are also exposed to a range of climatic temperatures at different times of the year (see Table 1 which shows the outdoor temperature a cow could be exposed to in different regions of the world).

Comment [u1]: Insert Table 1 near here

A controlled release implant would not be developed for a specific country, or a given time of the year, but rather, would be marketed worldwide. Thus the ear of a cow (a common place for the location of implants) could be exposed to ambient temperatures that range -13.1°C to 27.5°C (Table 1). The temperature of the surface of the ear of heifers over winter and summer periods was measured by Mader and Kreikemeier [4]. During the study winter and summer ambient temperatures averaged -2.9 and 26.7°C, respectively. Heifer body temperatures averaged 39°C and 38.9°C over each season, however, ear surface temperatures varied dramatically at 13.6 and 33.5 °C for

winter and summer, respectively. Such climatic influences might affect drug release from the implant.

These differences present numerous challenges to the pharmaceutical scientist charged with developing a new formulation for an animal. An in depth knowledge of formulation science, the physicochemical principles of pharmacy and biopharmaceutical aspects relating to the specific route of delivery result in optimal products tailored to meet demanding needs. These challenges have been discussed by numerous authors for a number of routes of drug delivery in the book edited by Rathbone and Gurny [5]

Sometimes dosage forms for animals are fundamentally the same as those in their human counterparts (e.g., injections and implants), whereas in other cases, the unique biological characteristics of the animal result in quite different outcomes (e.g., transdermal patches in humans versus spot-ons or pour-ons in animals). Nowhere is this difference more obvious, than in the area of controlled release technology, where different demands (e.g., very extended periods of delivery, e.g., months), administration site characteristics and variations in anatomy and physiology, result in dosage forms that simply cannot cross-over from animals to humans (e.g., rumen products).

The veterinary pharmaceutical industry has been a pioneer in the area of controlled release drug delivery technology through its development of commercially available products that incorporate an innovative mix of the pharmaceutical, engineering and polymer sciences [6]. It has played an

important role in the development of the animal health pharmaceutical industry [6] through its well designed controlled release drug delivery technologies that provide many advantages to the end user and provide a useful option with which to extend the patent life of a drug. However, despite these advantages, relatively few controlled release products are available on the veterinary market, and although many have been conceptualised (as evident from the extensive patent literature pertaining to this field), few actually reach the market. Indeed, many needs have been cited by authoritative authors within papers included in Special Theme Issues of the journals *Advanced Drug Delivery Reviews* and *Journal of Controlled Release* [7-13] and within companies for several decades now (e.g., biodegradable rumen products, pulsing rumen products, etc), but have yet to be achieved. This situation reflects the immense challenges associated with the development of a controlled release veterinary drug delivery technology. Many conceptual ideas simply do not perform as expected in the animal due to the complexity of the environment that the delivery system finds itself exposed to, resulting in unexpected effects on the delivery systems physical stability, release characteristics, polymer behaviour (both physical and chemical), etc. This situation reflects a lack of availability of fundamental knowledge on the various routes of drug delivery in the animal, behaviour of polymers (biodegradable and non-degradable), behaviour of excipients, and delivery system capability. The lack of fundamental knowledge in the area as it relates to drug delivery provides the opportunity for a formulation scientist in academia to develop research programs that conduct fundamental studies which provide foundational knowledge which other scientists can use to

advantage in their development of commercially useful controlled release veterinary drug delivery technologies.

Industry Challenges

Although the reasons for producing controlled release drug delivery technologies is the same as those in humans, the reasons for developing them are not [2]. For both human and animal applications controlled release drug delivery technologies are produced in order to permit delivery of an active in a form that is effective, safe and able to be handled and administered by the end user [2]. However, the reasons for developing a drug into a long acting delivery system for human use include the reduction of dose frequency in order to improve patient compliance, or to improve the efficiency of therapy and thereby improve the health of the patient. In contrast in the veterinary field, the major reasons for developing a drug into a controlled release drug delivery technology is to minimize animal handling in order to reduce the stress to animals and farmer from repeated administration, and to reduce the cost of treatment in terms of money and time spent by the end user on drug administration [2]. Thus the human field is focussed on improved outcomes for the patient. In contrast, the animal arena focuses on improved return on investment, easier farm management practices, reduced stress on the farmer and less animal handling. These fundamentally different reasons challenge the veterinary industry approach to the development of a controlled release drug delivery technology for production animals. Note that development of controlled release products for companion animals are in fact governed by

similar set of principles as for human medicine: premium-priced products for an individual precious family member [14].

The major challenges a veterinary pharmaceutical company faces when developing a controlled release veterinary technology for farm animals is a smaller overall commercial market, smaller profit margin and less research dollars with which to develop products. The final price of the product is crucial to its success and the product must be tailored accordingly. This requires prudent selection of excipients and polymers (must be cheap), manufacturing methods (must be efficient and cost effective) and need (a heavy responsibility on the marketing team). Although some of the development costs can be offset by a shorter clinical stage timeline to drug approval compared to human pharmaceuticals, taking advantage of this opportunity requires an experienced team focused on the task of product commercialisation.

The final cost of the product also represents a major challenge and determines the complexity of design, type and number of excipients and types of polymers that are used to formulate the product. Often this particular challenge results in a limited palette from which to paint.

The need for the product to fit within existing manufacturing capability and production processes is a further challenge. A poor fit within a company can stop efforts being made to develop a product, or to take a product idea

forward, due to the return on investment being adversely impacted by the need for upfront investment in manufacturing equipment.

The animals (the patient) are another challenge. The large number of species, the fact animals cannot talk and the great variety of physiological difference between (or even within some) species, results in the veterinary pharmaceutical industry opting to specialise in specific areas related to clinical condition and within that, animal types e.g., anthelmintics, cattle. Fully grown animals exhibit a wide range of weights. For example Beef cattle range 266-641 kg, dairy cows 600-700 kg and sheep 54-66 kg [6]. Animals also exhibit a wide range of weight differences throughout their life. Such variations between and within animals result in the challenge of needing more dosage form presentations (e.g., strengths, volumes) to treat the range of animals that could benefit from receiving the medication.

With respect to this challenge, the initial decision the formulation scientists faces is whether to develop a product that allows dosing per animal or one that allows dosing per weight of animal. If the former approach is chosen and a technology is developed that allows treatment on a per animal basis, this involves the challenge of incorporating a wide drug safety margin into the product. If the latter approach is chosen, then this results in the challenge of developing a delivery technology that is flexible enough to administer a range of doses to cover both different animals and even the growing animal. For some liquid dosage forms, for example injections, this can be achieved relatively easily by formulating the product to enable different volumes to

cover different animals or growing animals. However, the theoretical example shown in Table 2 [Foster, personal communication] shows that challenging decisions need to be addressed with regard to the strength of the formulation (based on corresponding volumes delivered) and this is compounded by the fact that the specific dose is not known until dose selection and confirmation studies have been conducted.

Comment [u2]: Insert Table 2 near here

For a solid controlled release veterinary technology this challenge can be more demanding, but is possible to address. It generally results in more complex registration procedures and increasingly complex stability trials. The TimeCapsule® range [15], for instance, comes in four different sizes in order to cover sheep and cattle throughout their different growth periods. Each one has different dimensions (diameter and length), and contains different amounts of active ingredient, but each consists of the same core technology: zinc oxide and excipients extruded into a bolus that is trimmed to shape and then covered by a waxy material (Fig. 1).

Comment [u3]: Insert Figure 1 near here

A second example is the CIDR® intravaginal insert [16-19] which comes in three sizes to cover sheep, cattle and pigs. The sheep and cattle insert consists of the same basic T shape, but differs in size, whereas the pig CIDR comprises a completely different shape (Fig. 2). Fundamentally, however, all three inserts are manufactured using the same technological principle, process and components: progesterone is homogenously dispersed within silicone and injection-molded over a rigid spine.

Comment [u4]: Insert Figure 2 near here

Another challenge to industry is the added need with food producing animals of ensuring no unsafe drug or metabolite residues exist in the food being consumed [2]. This involves extensive absorption, distribution, metabolism and excretion (ADME) studies and safety characterization. The need to undertake these studies for regulatory purposes adds to the cost of the product development program, which influences the price of the product and ultimately the end-user cost:benefit ratio. Thus, new polymers and novel excipients are rarely used in controlled release veterinary drug delivery technologies due to the additional metabolic /stability and animal toxicological studies that may be required to assure successful registration.

Another challenge is the means by which the dose is administered. In the animal arena the entire patient population needs assistance in the administration process. The solution to this problem falls on the formulator who must incorporate the design of purpose built applicators and remember to incorporate this aspect within the development of their delivery system. Thus the maximum size of any veterinary delivery system, for example, may not simply be determined by the anatomical constraints of the animal, but rather by the physical dimension of the administration device, which in turn is related to the ability of the owner/farmer to use it at a practical level [20,21]. This provides a formulation challenge in that the final dosage form is often much smaller than the formulation scientist first envisages, resulting in lower dose loading capacity and fewer capabilities of the delivery system than first imagined [21].

The scientific challenges faced by industry are many. Several books and theme Issues of Journals are available that expound on these challenges [5, 7-13, 22]. Each product that is developed must exhibit acceptable safety, efficacy and stability profiles, each feature being built into the product and addressed with the additional challenge; that of residual drug remaining at the administration site. Safety aspects apply to both the user and the animal. Efficacy trials will involve many more participants compared to human trials, and must often encompass different breeds, seasons and geographical locations to evaluate the effect of these on product efficacy. Chemical stability can be a major issue. Farms do not have specialised areas for storage of pharmaceuticals (cold storage facilities or air conditioned sheds), therefore assuming that a product can be stored below 20°C or in the fridge for the duration of its lifetime prior to administration is an unreasonable assumption for farmed animal products. The physical stability profile of the product is an interesting challenge. A farmer is less interested in what the product looks like compared to its efficacy profile, ease of use, ease of administration, ease of removal, tissue residue profile and time it takes to herd, administer and release his animals back into the paddock [2]. Veterinary formulation scientists may, for example, have to trade off pharmaceutical elegance to improve other features such as ease of administration, provided the efficacy and safety profile is acceptable and not altered during storage.

A further challenge is the impact that the delivery technology has on the environment. In essence, the animal's toilet is the environment, and it is a

regulatory requirement to assess and determine the impact of the new technology on ecosystems. This adds time and cost to the development and commercialization of a controlled release veterinary technology.

The future also holds the potential challenge to become involved in the reduction of carbon footprints by manipulating carbon dioxide and methane emissions from cattle arising from their belching. According to a report published by the United Nations Food and Agriculture Organization, cattle farming is a significant contributor of greenhouse gases [23]. Reduced emissions can be manipulated through food intake [24], however, in the future new drugs will be developed that achieve this goal and these will need specialized controlled release dosage forms to effectively deliver them in a predefined manner to maximize effect.

The market represents a further challenge. Identifying needs is one thing; identifying needs that can return a profit on years of research investment is another. Animal health products cover a range of pharmaceuticals, vaccines, medicated feed additives and nutraceuticals. This presents challenges with differences in the physicochemical properties of these compounds and their different formulation requirements. Also, over the last decade the farmed animal area has remained fairly flat with less real dollars spent on R&D with an impact of less product line extensions via drug delivery as a consequence. In contrast, the companion animal market has seen market growth as it is considered to more lucrative. In 1986, at least in the UK, 70% of veterinary products were marketed for livestock, but in 2008 just 45% of sales were for

that market. In contrast the UK companion sector had grown to 52% of the total market, driven by growth in vaccines and novel medicines for that sector [25]. Industry focus on companion animal products has resulted in quite different needs in terms of the type of scientists undertaking that work. The companion animal industry has moved away from employing the specialist farmed animal formulation scientist in favour of highly capable formulation scientists with human product development experience. Existing farmed animal experts have either moved out of the animal arena or have adapted and developed their skills to work within, say, the injectable, liquid or tablet specialties. Consolidation of companies has reduced the amount of R&D dollars spent on discovering new molecules resulting in fewer new chemical entities being discovered and approved for veterinary medicine. A further effect of this difficult commercial environment is that expertise in this area is diminishing since most pharmaceutical scientists are drawn to the more lucrative and stable human market.

A further challenge is regulatory needs. The regulations as they relate to the pharmaceutical science component of product development are the same regardless of whether they are developed for human or veterinary application. Final manufacturing GMP requirements are identical whether the product is manufactured for animal or human use and it is noticeable that many Pharma manufacture their animal health products in the same facilities as their human health care drugs.

An curious challenge that has arisen in recent times arises from the consolidation of farms which has been a trend in the USA for certain species such a swine and chickens. This impacts on companies world-wide as, for certain species, the profitable US market becomes controlled by only a few large farms. In effect this means that if the pharmaceutical company cannot get those farms to buy their new product, then they will not be able to recoup their investment.

These represent but a few of the challenges a profit-driven company faces when developing a controlled release drug delivery technology. In order to become lucrative and competitive in this challenging market environment the market has seen the consolidation of large companies with several mergers or takeovers occurring over the last decade.

Industry Opportunities

Despite the challenges facing the veterinary pharmaceutical industry, several opportunities exist.

The time to market can be shorter compared to human pharmaceuticals. This opportunity can be exploited to advantage through the employment of an experienced product commercialisation team who can rapidly complete development activities. If the time to market can be minimised, income begins quicker through the exploitation of market opportunities and more profits can be made before the patent protection on the technology expires.

Another opportunity is that animals are more readily available to conduct research on than humans. Early ADME research can be conducted, especially in food producing animals, which can often aid the formulation development. This opportunity allows experiments on target species to be conducted at an early stage in the research process, and continue throughout the development phase. The outcome is that ideas can be quickly tested, and bench concepts confirmed in the species for which the product is ultimately intended. Indeed, the entire research and development clinical phase program can be conducted in the species for which the product is intended. Another opportunity for the veterinary pharmaceutical industry is that human drugs need to be tested first in animals thus a wealth of safety and toxicological, as well as pharmacological data is often available on a particular drug or its derivatives in animals (particularly dogs). This offers the veterinary industry the opportunity of “hand-me downs”. Indeed, one approach in recent times has been for veterinary pharmaceutical companies to search through the files of companies that synthesize drugs for second tier drug derivatives that are already synthesized and possess known safety and toxicological profiles that have already been tested in potential target species (e.g., dogs) and develop strategies to bring these to market. To date, examples of leverage have been seen in the companion animal market and include the recent marketing of reformulated human serotonin-selective reuptake inhibitors and monoamine oxidase-B inhibitors for dogs with separation anxiety and cognitive disorders respectively [26,27]. Fluoxetine and selegiline

were tested in dogs during the preclinical phase of their development as eventual human products many years ago [26].

A further opportunity arises from the need for environmental assessment which is required for registration purposes (already discussed under challenges). The opportunity is that the knowledge gained from environmental assessment studies can aid formulation development because of the need to undertake and understand degradation processes of the drug and its delivery system (temperature, light, pH).

Currently there is a lack of new (APIs) appearing on the veterinary market, although there are some examples of new compounds reaching the farmed animal market e.g., [28]. In the short term this problem can be offset by developing controlled release drug delivery technologies to extend the commercial life of existing drugs. Although the development of a controlled release veterinary drug delivery technology represents an ongoing challenge, it does present a major opportunity. The farmed animal industry places a high value on delivery technologies that can lower the overall cost of treatment, improve ease of administration, improve efficacy and avoid the use of needles [29].

Academic Challenges

The academic scientist who chooses to apply pharmaceutical science to the research of veterinary pharmaceuticals faces many challenges. There may

be questions on the relevance of conducting such research within a Pharmaceutics Department whose academic teaching and research program is focussed on human health. There are also questions on how funding for such research will be attained. The answer is that the same science is involved in the research of veterinary pharmaceuticals and controlled release technology as those of their human counterparts, allowing interdepartmental cross-over of expertise, knowledge and learnings. The synergy between pharmaceutical scientist and veterinary/animal scientists based in Veterinary and Agriculture Departments is obvious, and with outcomes being heavily industry focussed allowing for the attraction of company interest in the collaborative research programs. Such collaborations and synergies will only strengthen grant applications and potentially result in more successful funding rounds.

Lack of expertise surrounding the academic is also a challenge to the scientist working on veterinary formulations. Although, as pointed out above, their surrounding colleagues provide inspiration and knowledge due to the cross-over of the fundamental pharmaceutical sciences involved in the research and development of veterinary products, specialist knowledge is still required and the inspiration and valued discussion with other experts on veterinary product specific issues is valuable but the opportunity is lacking in most departments.

Funding is an on-going issue for the academic scientist who chooses to apply pharmaceutical science to the research of veterinary pharmaceuticals.

Governments are actively promoting industry-academic relationships, so

opportunities for Schools of Pharmacy and/or Animal Science academic researchers to leverage translational applied drug delivery research provides a great opportunity. For example, Pfizer Animal Health are partners in a major grant worth over 7 million Euro over 5 years in farm animal reproduction funded by Science Foundation Ireland at University College Dublin [30].

Veterinary pharmaceutical scientists based in universities cannot however, rely on animal pharmaceutical companies for sufficient direct funding. In addition grant applications from relevant Government agencies may be limited in scope, quantity and size. There are hybrid-type opportunities under various State enterprise schemes in the European Union whereby a State grant might pay the stipend of a PhD candidate or post-doctoral researcher, while the company pays for the consumables directly or in an “in-kind” contribution. To counteract this, academics need to spread themselves wider by also generating hypotheses relevant to human health and to human Pharma as this will increase potential funding sources.

In Australia and New Zealand, companies are encouraged to form collaborations with academia though the availability of grants that provide funding for commercial outcome projects. In New Zealand the Foundation for Research, Science and Technology (FRST) invests almost \$500 million a year in science and technology research on behalf of the New Zealand Government [31]. The FRST Technology Fellowship scheme encourages innovative companies to involve postgraduate students in their research and

development programmes [31]. The ultimate aim is to facilitate the company to develop new knowledge that leads to the commercialization of a new product, process, or service, which grows their revenue. Another FRST funding opportunity is entitled Research Consortia [31]. This provides funds for industry groups to complete significant, longer-term research contracts in partnerships – including academic institute partners. The consortium must invest a minimum of \$500,000, which the Foundation will match on a dollar-for-dollar basis up to \$2.5 million per annum. FRST also offers funding to support students and scholars and invests approximately \$7.0 million per annum in fellowships for students and scholars to undertake science and technology research.

In Australia the Australian Research Council (ARC) offers funding opportunities to foster university and industry interaction [32]. Specifically, the Collaborative Research Grants (CRG) Scheme and the Australian Postgraduate Awards (Industry) represent two opportunities to build industry and university research alliances, resulting in industry focused research training of a potential future employee. The scheme offers industry partners the opportunity to resolve their particular industrial problem, while simultaneously engaging academic researchers [32].

Funding opportunities that promote collaborative research between academia and industry serve to build closer alliances between these two sectors. The industry partner receives a solution to their problem, access to specialist expertise, an improved capacity to solve problems and development of a

more enduring relationship with universities. It also provides them with the opportunity to engage in basic scientific research in a collaborative, rather than contract, relationship. The student benefits because they have the opportunity to conduct at least some of their research at the company within a commercial environment thereby gaining valuable commercial research and development expertise. Academic partners are rewarded with the opportunity to conduct useful research and apply their ideas in an industry context, to train postgraduate students, and to extend their interactions with industry. Ultimately the interaction provides the opportunity for activities that translate research into veterinary health, welfare and production improvements resulting in enhanced economic prosperity.

Lack of appropriate manufacturing equipment represents another challenge. Many veterinary products revolve around injection moulding, and such equipment is rarely available within Schools of Pharmacy. Establishing collaborations with injection moulding-type companies are possible but challenging: these include a limit as to what and how many drugs can go through their facility, contamination issues, drug containment issues, the number of times one can use company facilities, lack of complete control over manufacturing process and parameters, inability to fully optimise machine settings, the quality of product produced, the need for large runs (large machines resulting in the need for large amounts of raw material). This list represents just some of the challenges that the academician will face.

Interest in the veterinary pharmaceutical arena from students is another challenge. Students will be preferentially attracted to research projects in the more lucrative human industry projects. There is a need for the academician to sell innovation as a quality, that the same science applies to both human and veterinary areas, that the student will be exposed to more of the overall development process (will be exposed to animal studies faster), that cross-over of experiences gained during veterinary product development are equally applicable to human product development, there is more possibility of seeing product on the market compared to human, that they will become a generalist versus a specialist in the area of pharmaceutical science. Pharmacy and veterinary undergraduates are however, very difficult to attract into Ph.D programmes as the majority wish to start earning professional salaries upon graduation. The default position is to hire graduates from the biosciences, chemistry or engineering programmes as Ph.D. candidates. While they do not have direct experience of pharmaceutical formulation and development processes, many are better trained in scientific method and hypothesis generation.

All these challenges face the academic scientist who chooses to apply pharmaceutical science to the research of veterinary pharmaceuticals, however, every challenge can be viewed as an opportunity within academic environment and can be exploited and used to advantage.

Academic Opportunities

In contrast to the industrial landscape, the outlook for an academic veterinary pharmaceutical scientist is quite different. From an academic perspective, when you remove the commercial requirement associated with product innovation and development, there are a myriad of fundamental and applied research opportunities. These include: Characterisation of different administration sites as routes for drug delivery providing information to facilitate product design, identifying dosage form limitations, characterising excipients and defining formulation possibilities; Testing and demonstrating the clinical usefulness of different delivery regimes (continuous versus pulsed versus chronological); Study of drug transport biology; Evaluating the suitability of new polymers and excipients as delivery platforms and; The provision of a research laboratory for rapid screening of ideas and concepts. In essence, since money is not a concern – more expensive excipients can be used, more expensive polymers can be utilised, more sophisticated approaches can be tried, more complex delivery technologies can be conceptualised and tested...and the outcome of demonstrating the potential worth, or otherwise, of an approach is sufficient to achieve the academicians goal...a publication.

Veterinary drug delivery is a scientifically interesting area. The diverse range of animals, with their corresponding breed differences and anatomical and physiological differences, offers the inventive and innovative scientist the opportunity to invent and explore drug delivery possibilities beyond those experienced within the human industry. It provides them with an opportunity to apply their extensive physical pharmacy knowledge, in combination with

biopharmaceutical principles, to the development of unique dosage forms. Novel applications of conventional manufacturing techniques together with inventive applications and use of excipients and common polymers, offers an opportunity to invent, apply and use their knowledge. Immediate access to animals provides a unique insight into product performance in the target animal species making conclusions and product optimization decisions more relevant than those generated through bench studies. Data in the target species also allows for the development of in vitro drug release models that are representative, predictive and correlate to the in vivo performance of the delivery system. In some cases, differences in release mechanisms can be observed, providing academic stimulation and challenge [33].

Another academic opportunity arises from the use of the controlled release drug delivery technology as a research tool. Increased collaborations, increased knowledge through the study of physiological and endocrinological responses that result from the different release profile and subsequent plasma profiles leading to different biological effects [34] can provide another academic opportunity. The capability to administer multiple drugs in a controlled way, either as pulsed delivery or in a precisely controlled manner at different drug concentrations or rates of delivery offer many investigative opportunities. The administration of different drugs not formulated into commercial preparations provides yet another research opportunity.

Opportunities in comparative physiology and pharmacology also exist. For example, human companies favour academics with a good understanding of

animal comparisons with man, particularly companion animals. In addition, drug transport biology appeals to animal and human health companies alike providing an example of the advantage of developing research tools with wide applicability. Further opportunities for the academician lie within the Agri-food industry. There are new formulation opportunities to develop prebiotics and probiotics for veterinary species [35], where formulation expertise is usually lacking. In addition, a major evolving international research area is that of developing functional foods and pharmaceuticals from natural dairy products including components of milk and cheeses [36]. There is also some funding available from Government agencies in reducing carbon footprints of production animals and many academics are getting funds for changing the diet of cattle to reduce methane emissions as part of an attempt to adhere to the Kyoto Agreement [24]. These are all potentially profitable areas for the academic pharmaceutical scientist with skills in formulation and controlled release science and technology.

Concluding Remarks

The Animal Health market represents an area of the pharmaceutical industry that is smaller, has less total resources spent on it and offers less rewards compared to its human counterpart. The industry faces many issues, not the least of which is that currently there is a lack of new APIs appearing on the veterinary market. In the short term this problem can be offset by developing controlled release drug delivery technologies to extend the commercial life of existing veterinary drugs. However, such a commercial opportunity does not

come without its challenges. These generally revolve around money – the limited budget assigned to conduct R&D, the cost competitive amount that can be charged for the finished product and costly registration processes. A further effect of this difficult commercial environment is that limited expertise exists in this area since most pharmaceutical scientists are drawn to the more lucrative and productive human market. It is not surprising therefore that few controlled release products appear on the market, despite their potential advantages to the farming industry.

Overall, therefore, studying veterinary controlled release drug delivery as an area of research within an academic environment opens up the opportunity to investigate a wider range of possibilities and propose a greater number of solutions compared to an industry based researcher focussed on getting a formulation approved. The aim of such research would be to provide others the opportunity to learn from the experiences of the academician through the publications that arise from such studies. Finally, novel intellectual property developed in the university sector in the area of veterinary controlled release can to be protected and either be the source of a spun-out start-up company or alternatively licensed onto industry

References

1. Hunter, R.P.; Isaza, R. Zoological pharmacology: current status, issues and potential. *Adv. Drug Del. Rev.*, **2002**, *54*, 787-793.
2. Rathbone, M.J.; Foster, T.P. In *Modern Pharmaceuticals. Applications and Advances*; A.T. Florence and J. Siepmann, Eds.; Informa Healthcare: USA, **2009**; Vol. 2, pp. 293-328.
3. Source: <http://www.worldclimate.com/>.
4. Mader, T. L.; Kreikemeier, W.M. Effects of growth-promoting agents and season on blood metabolites and body temperature in heifers. *J. Anim. Sci.*, **2006**, *84*, 1030-1037.
5. Rathbone, M.J.; Gurny, R. *Controlled Release Veterinary Drug Delivery: Biological and Pharmaceutical Considerations*, Elsevier Science B.V: Amsterdam, **2000**.
6. Ahmed, I.; Kasraian, K. Pharmaceutical challenges in veterinary medicine product development. *Adv. Drug Del. Rev.*, **2002**, *54*, 871-882.
7. Rathbone, M.J. (Theme Editor). Veterinary Drug Delivery. Part I. Special Theme Issue. *Advanced Drug Delivery Reviews* **1997**, *28*, 91 pages.
8. Rathbone, M.J.; Cady, S.M. (Theme Editors). Veterinary Drug Delivery Part II. Special Theme Issue. *Advanced Drug Delivery Reviews*. **1998**, *38*, 83 pages.
9. Rathbone, M.J.; Witchev-Lakshmanan, L. (Theme Editors). Veterinary Drug Delivery Part III. Special Theme Issue. *Advanced Drug Delivery Reviews*. **2000**, *43*, 92 pages.

10. Rathbone, M.J.; Witchev-Lakshmanan, L. (Theme Editors) . Veterinary Drug Delivery Part IV. Special Theme Issue. *Advanced Drug Delivery Reviews*. **2001**, 50, 147 pages.
11. Rathbone, M.J. (Theme Editor). Veterinary Drug Delivery Part V. Special Theme Issue. *Advanced Drug Delivery Reviews*. **2002**, 54, 97 pages.
12. Rathbone, M.J.; Martinez, M.M. (Guest Editors). Veterinary Drug Delivery Part VI. Special Theme Issue. *Advanced Drug Delivery Reviews*. **2004**, 56, 182 pages.
13. Rathbone, M.J.; Bowersock, T. (Theme Editors). Veterinary Drug Delivery (Special Issue) *J. Control. Rel.*, **2002**, 55, 284 pages.
14. Oudot, E.M.; Baird, A.W.; Brayden, D.J. In *Handbook of Experimental Pharmacology: Comparative and veterinary pharmacology*; Cunningham. F.; Elliott, J.; Lees, P. Eds.; **2009**.
15. R Munday, R.; Thompson, A.M.; Fowke, E.A.; Wesselink, C.; Smith, B.L.; Towers, N.R.; O'Donnell, K.; McDonald, R.M.; Stirnemann, M.; Ford A.J. A zinc-containing intraruminal device for facial eczema control in lambs. *N. Z. Vet. J.*, **1997**, 45, 93-98.
16. Rathbone, M.J.; Macmillan, K.L.; Inskip, K.; Day, M.; Burggraaf, S.; Bunt, C.R. Fertility regulation in cattle (Invited Review). *J. Control. Rel.*, **1997**, 54, 117-148.
17. Rathbone, M.J.; Macmillan, K.L.; Jöchle, W.; Boland, M.; Inskip, K. Controlled release products for the control of the estrous cycle in cattle, sheep, goats, deer, pigs and horses (Invited Review). *Crit. Rev. Ther. Drug Carr. Syst.*, **1998**, 15, 285-380.

18. Rathbone, M.J.; Kinder, J.E.; Fike, K.; Kojima, F.; Clopton, D; Ogle, C.R.; Bunt, C.R. Recent advances in bovine reproductive endocrinology and physiology and their impact on drug delivery system design for the control of the estrous cycle in cattle. *Adv. Drug Del. Rev.*, **2001**, *50*, 277-320.
19. Rathbone, M.J.; Bunt, C.R.; Ogle, C.R.; Burggraaf, S.; Ogle, C.; Macmillan, K.L.; Burke, C.R.; Pickering, K.L. Reengineering of a commercially available bovine intravaginal insert (CIDR insert) containing progesterone. *J. Control. Rel.*, **2002**, *85*, 105-115.
20. Cook, D.W. In *Development and formulation of veterinary dosage forms*; Hardee, G.E; Baggot, J.D., Eds; Marcel Dekker Inc.: New York, **1998**; Vol. 88, pp. 305-356.
21. Rathbone, M.J.; Burke, C.R.; D.J.; Ogle, C.R.; Bunt, C.R.; Burggraaf, S.; Macmillan, K.L. In *Controlled Release Veterinary Drug Delivery: Biological and Pharmaceutical Considerations*; Rathbone, M.J.; Gurny, R. Eds.; Elsevier Science B.V; Amsterdam, **2000**; pp. 173-200.
22. Hardee, G.E; Baggot, J.D. *Development and formulation of veterinary dosage forms*, Marcel Dekker Inc.: New York, **1998**.
23. Steinfeld, H.; Gerber, P.; Wassenaar, T.; Castel, V.; Rosales, M.; de Haan, C. Livestock's long shadow: Environmental issues and options. Food and Agriculture Organization of the United Nations. Rome. **2006**. <http://www.fao.org/docrep/010/a0701e/a0701e00.HTM>
24. Foley P.A.; Kenny D.A.; Callan J.J.; Boland T.M.; O'Mara F.P. Effect of DL-malic acid supplementation on feed intake, methane emission, and rumen fermentation in beef cattle. *J. Anim. Sci.*, **2009**, *87*, 1048-1057.

25. Source: National Office of Animal Health,
UK: http://www.noah.co.uk/focus/facts_figures.htm.
26. Simpson, B.S.; Landsberg, G.M.; Reisner, I.R.; Ciribassi, J.J.; Horwitz, D.; Houpt, K.A.; Kroll, T.L.; Luescher, A.; Moffat, K.S.; Douglass, G.; Robertson-Plouch, C.; Veenhuizen, M.F.; Zimmerman, A.; Clark, T.P. Effects of reconcile (fluoxetine) chewable tablets plus behavior management for canine separation anxiety. *Vet. Ther.*, **2007**, *8*, 18-31.
27. Landsberg, G. Therapeutic options for cognitive decline in senior pets. *J. Amer. Anim. Hosp. Assoc.*, **2006**, *42*, 407-413.
28. Kaminsky, R.; Ducray, P.; Jung, M.; Clover, R.; Rufener, L.; Bouvier, J.; Schorderet, S.S; Wenger, A.; Weiland-Berghausen, S.; Goebel, T.; Gauvry, N.; Pautrat, F.; Skripsky, T.; Froelich, O.; Komoin-Oka, C.; Westlund, B.; Sluder, A.; Maser, P. A new class of anthelmintics effective against drug-resistant nematodes. *Nature*, **2008**, *452*, 176-181.
29. Steadman, D.F. Drug delivery technologies: Market forces in veterinary medicine. *Anim. Pharm. News.*, **2008**, *April*, 21,22.
30. Source: http://www.ucd.ie/agfoodvet/reproductive_biology.htm.
31. Source: <http://www.frst.govt.nz/>
32. Source: <http://www.arc.gov.au/>
33. C. Ogle. "Characterisation of the pharmaceutical, structural and mechanical properties of an intravaginal drug delivery device". PhD Thesis. University of Waikato. **2000**.
34. Rathbone, M.J.; Macmillan, K.L. Applications of Controlled Release Science and Technology: Progesterone. *Controlled Release Newsletter*, **2004**, *21*, 8-9.

35. Wynn, S.G. Probiotics in veterinary practice. *J. Amer. Vet. Med. Assoc.*, **2009**, 234, 606-613.
36. Ebringer, L.; Ferencík, M.; Krajcovic, J. Folia. Beneficial health effects of milk and fermented dairy products review. *Microbiol (Praha)*, **2008**, 53, 378-394.

Tables

Table 1. Summer and winter 24 hour average temperature variations around Australia and the world. Data from reference [3].

City	Country	24 hour average temperature	
		Winter	Summer
Brisbane	Australia	15.4 ¹	24.7 ²
Hobart	Australia	8.3 ¹	16.0 ²
Cairns	Australia	19.7 ¹	27.5 ²
Hamilton	New Zealand	4.4 ¹	27.0 ²
Buenos Aires	South America	10.5 ¹	21.6 ²
Capetown	South Africa	12.9 ¹	20.7 ²
Edmonton	Canada	-13.1 ²	14.7 ¹
Madison	USA	-2.4 ²	27.0 ¹
Beijing	China	-3 ²	25.1 ¹
Exeter	England	5.9 ²	16.1 ¹

¹June, July, August.

²December, January, February.

Table 2. Theoretical example of an injectable API with a dose of 1 mg/kg showing the effect of concentration on the amount of product that must be administered to achieve a therapeutic dose.

Species (Weight)	Amount of 0.1%	Amount of 1%	Amount of 10%
Sheep (40 kg)	40 mL	4.0 mL	0.4 mL
Cattle (300 kg)	300 mL	30.0 mL	3.0 mL

Figure 1. Some of the available sizes and shapes of the TimeCapsule® range manufactured using the same core technology that allows it to be produced in different sizes for use in sheep and growing cattle.

Figure 2. CIDR intravaginal inserts for cattle (upper left), sheep (upper right) and pigs (bottom) showing shape and size differences between products.