

## Delivering drugs to farmed animals using controlled release science and technology

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**Abstract:** This article presents an overview of long acting products used in animal health, production and reproduction. The topic represents a niche field of controlled release that few formulation scientists become specialists and experts in, but it is a field which has made significant contribution to the area of controlled release technology, and one which is of major importance to human kind due to their dependence on farmed animals as a source of hide, protein, milk and eggs.

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### Introduction

Conventional dosage forms are typified by tablets, capsules, suspensions, etc. Following administration, such dosage forms immediately expose the drug to dissolution and subsequent absorption. The appearance of the drug in the blood is typically rapid and sustained for only a short duration depending upon the half-life of the drug. In contrast controlled release drug delivery is a specialised area of pharmaceuticals dealing with formulating the drug in such a way that the formulation causes the entrapped drug to slowly release resulting in a long action for the administered drug. In most cases, the physicochemical properties of the long acting formulation control the resultant blood profiles as opposed to the innate properties of the drug. Controlled release formulations offer many advantages.<sup>1-3</sup> These will be highlighted later in this paper but, sufficient to say, there is no other field in pharmacy that derives more benefits from the advantages of controlled release technology than the farmed animal arena.

In the past 40 years, many long acting veterinary drug delivery technologies have been developed specifically for use in animals. These advancements have led to improvement of veterinary practice, animal welfare,

animal management practices such as reproduction, and the improvement of the treatment of diseases affecting farmed animals.<sup>1,2</sup> Examples include implants for cattle containing norgestomet (Syncromate-B) and oestradiol valerate (Crestar), intravaginal inserts containing progesterone in inert silicone (e.g., PRID and CIDR), intravaginal polyurethane sponges containing progestins, intraruminal bolus containing minerals or trace nutrients, antibiotics, growth promoting agents and anthelmintics using products (such as Ivomec bolus, Paratect Flex, Captec device, and TimeCapsule).<sup>3</sup>

The animal health market is complex and influenced by limited budgets for R&D, the amount that can be charged for the finished product and the expensive time-consuming product registration process.<sup>4-6</sup> This paper will present an overview of the area and discuss the current trends that are occurring and which influence this rapidly changing area of pharmaceutical research.

### Farmed animal health market landscape

In 2005 the world animal health market was worth US\$17.5 billion; in 2009 it had grown to about 19.2 billion.<sup>7</sup> If this trend continues, by 2020 predictions estimate that the world animal health market will surpass US\$30 billion. By sales the animal health market comprises approximately 60% farmed animal and 40% companion animal. In terms of species the farmed animal market is made up of cattle (45%), pigs (27%), poultry (19%), sheep (8%) and other (1%) (Figures for 2008). The world animal health market can also be classified into product groups. This description shows that vaccines/biologicals, pharmaceuticals (small molecules) and feed additives share 25%, 63% and 12% market share, respectively.<sup>7,8</sup>

In recent years the farmed animal health industry landscape has undergone significant change. In an attempt to be the number one in the area, numerous acquisitions and mergers have occurred resulting in several of the big players in the veterinary pharma industry merging. These changes have been facilitated by collaborations or licensing agreements with small companies holding

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patent protected technologies for niche markets. Indeed, such partnerships and alliances have become the core of a new business strategy for big pharma.

### **Advantages, challenges and opportunities**

Long acting veterinary dosage forms offer many advantages. The biggest advantage is reduced stress levels in the animals associated with less frequent dosing and reduced handling. In addition other advantages include reduced cost of treatment, less stress to the workers, improved herd management, as well as patent protection for the product innovator and extension of the product life cycle.

The challenges to developing a long acting product and, ultimately, using a long acting product in the daily regimen of a farmed animal are numerous.<sup>2,3</sup> These revolve around the issues of efficacy, retention, administration and removal of the products to patients that are large and awkward to handle, have the potential to cause unintentional harm to the user, and provide limited opportunity for self-medication. All this in an environment in which hundreds of animal are owned by (and therefore need treatment from) a single owner, are free roaming (and therefore need herding before administration), where dosing is defined as dose/kg body weight (and animals vary in weight both within and between species), and are maintained within a business environment (therefore cost is a major consideration of treatment). Add onto this, the fact that high drug loads need to be delivered, the resultant products are large and require some form of administration method, the product needs some retention mechanism built into its design and the concern for human food safety (tissue residues) and you can begin to appreciate the demands facing the formulation scientist in this challenging area of pharmaceutical science.

### **Design challenges**

Farmed animals do not have the ability to self-administer veterinary drug delivery systems. Therefore veterinarians and producers need some means by which

to easily (and without causing harm, pain or damage to the animal) administer veterinary products.<sup>3</sup>

This is achieved through the use of applicators: instruments designed to allow loading of the product into it at one end and easy release of the product into the site of administration through the use of some release mechanism that is operated by the person administering the product. These applicators are referred to as balling guns (for rumen products), applicators (for intravaginal products) and implanters (for subcutaneous implants).<sup>3</sup>

A veterinary product will only be effective if it remains at the site of administration/absorption for the duration of the treatment period. Poor retention rates reduce the overall efficacy of treatment. Rumen products are maintained in the rumen of farmed animals either through its innate geometry or by the addition of density agents.<sup>9</sup> Intravaginal veterinary drug delivery systems utilize an 'expansion mechanism' to retain the device in the vagina for the duration of treatment. In both cases, the products remain in the animal for the duration of treatment whether this is 7-10 days for intravaginal products, or up to 12 months for ruminal products.<sup>9</sup>

Since the majority of products administered to farmed animals are not biodegradable they require some means of removal from the animal at the end of the treatment period. Removal must be a simple process, be non-invasive (not require surgery) and be achieved quickly, safely and without damage to the animal. Typically removal of vaginal devices is aided by the addition of a 'tail' into the design of the device.<sup>10</sup> The tail should not interfere with any administration process, be long enough to protrude out of the vulva after the insert has been administered and extrude sufficiently so that an end user can grasp it firmly enough to pull the device out of the vagina without slippage.<sup>10</sup> The tail is usually made of a plastic, blue in color and curved so that it hugs the contour of the rear end of the animal.<sup>10</sup> Interestingly rumen products are never removed after treatment. They remain inside the rumen for the life of the animal. Indeed, 6-10 spent devices can be found in the animal's rumen at slaughter.

The size and shape of an intravaginal or ruminal drug delivery system is complex and dictated by the need for the insert to be flexible, change shape, expand or contract, depending upon the designers' intended administration and retention mechanism.<sup>9,10</sup> The key considerations in the final design revolve around it being safe to use and not cause damage to the animal upon insertion, while in place and during removal.

In general a characteristic of a veterinary product is its high drug load. Intravaginal delivery systems are also characterized by poor dose utilization which leads to a high residual content after removal. In contrast, ruminal products exhibit a high (100%) drug utilization.

### Literature in this area

A number of books and Special theme Issues of Journals have been published to capture the science and technology associated with this fascinating area of controlled release.<sup>3,11-20</sup> The reader is referred to these publications to gain a better appreciation of the complexity of the area and for some guidance on how to formulate, research and develop a veterinary long acting dosage form.

### Anatomy and physiology of the farmed animal

The anatomical and physiological features of the skin of an animal is similar to that of its human counterpart.<sup>21,22</sup> The major difference resides in the fact that animal skin is densely covered in hair. On the one hand this may be exploited for drug delivery, but on the other presents challenges when applying patches to the skin of farmed animals.

The vaginal cavity of the farmed animal is similar to that of a human and is a virtual space. It has different dimensions dependent upon the species and size of the animal and rests in the horizontal as opposed to the near vertical orientation of the human vagina. Ring shaped devices, that are commonly used in humans, were shown to be unable to be retained in the vagina of animals. Typically 'T' and 'Y' shaped delivery systems are used in animals.<sup>10</sup>

The anatomy and physiology of the gastrointestinal tract of farmed animals is complex and contrasts markedly to that of the human.<sup>9</sup> Cattle, sheep and goats are ruminants, whereas pigs are monogastrics and have a gastrointestinal tract similar to that of humans. Ruminant animals will be considered further in this section since an understanding of their anatomy and physiology provides the formulator with an insight not only into the challenges they will face but also the opportunities they can exploit.

The stomach of ruminants has four compartments. These are the rumen, reticulum, omasum and abomasum.<sup>9</sup> The rumen is the largest of the four compartments and has a structure that is conducive to drug delivery. Interestingly, the rumen is not a good site for absorption (since the rumen mucosa comprises of stratified squamous epithelium), therefore its value to the formulation scientist is in its ability to act as a compartment that can locate and retain a long acting drug delivery technology. In this respect, the rumen is large enough to accommodate a delivery technology, indeed, it can simultaneously contain multiple delivery technologies. In fact, the factor that limits the size of the delivery technology is not the size of the rumen, but rather its ability to be administered via the mouth and esophagus.

The rumen is essentially a large fermentation chamber ( $\pm 125$  L), providing an anaerobic environment, constant pH and temperature, and good mixing. It is an environment that will produce forces on a delivery technology that are strong enough to cause erosion or abrasion. All these features can be used to advantage by the pharmaceutical scientist.

Ruminant animals have evolved to consume and subsist on grasses and shrubs composed predominantly of cellulose. Therefore cellulosic pharmaceutical excipients that are commonly utilised in the human field to delay the rate of release of a drug (e.g., hydroxypropylmethyl cellulose) cannot be used in ruminal drug delivery technologies as the excipient will be rapidly digested.

Ruminants produce vast quantities of saliva. For adult cows volumes are in the range of 100 to 150 L of saliva per day. As a result the rumen contains ample water to facilitate drug release from a long acting veterinary dosage form.

### **Physicochemical principles of controlled release veterinary pharmaceuticals**

The physicochemical properties of a drug<sup>23,24</sup> affects its ability to be formulated, dictates selection of excipients, influences the rational selection of incoming raw material tests to assure its suitability for use in the final product and provides the rationale for its assessment and evaluation during development and post manufacture (i.e., the product's quality attributes). The physicochemical properties of a drug are an important consideration from pre-formulation to final product quality control. Knowledge of the physicochemical principles of pharmacy is the cornerstone of product research and development for veterinary pharmaceuticals as it is for human drug products.

The basic physicochemical principles that underpin veterinary product development are the same as those applied to human product research and development. The difference resides in the outcome of the application of that science; products for farmed animals are very large, exhibit a variety of shapes not encountered in their human or small animal counterparts and contain high amounts of active ingredient.

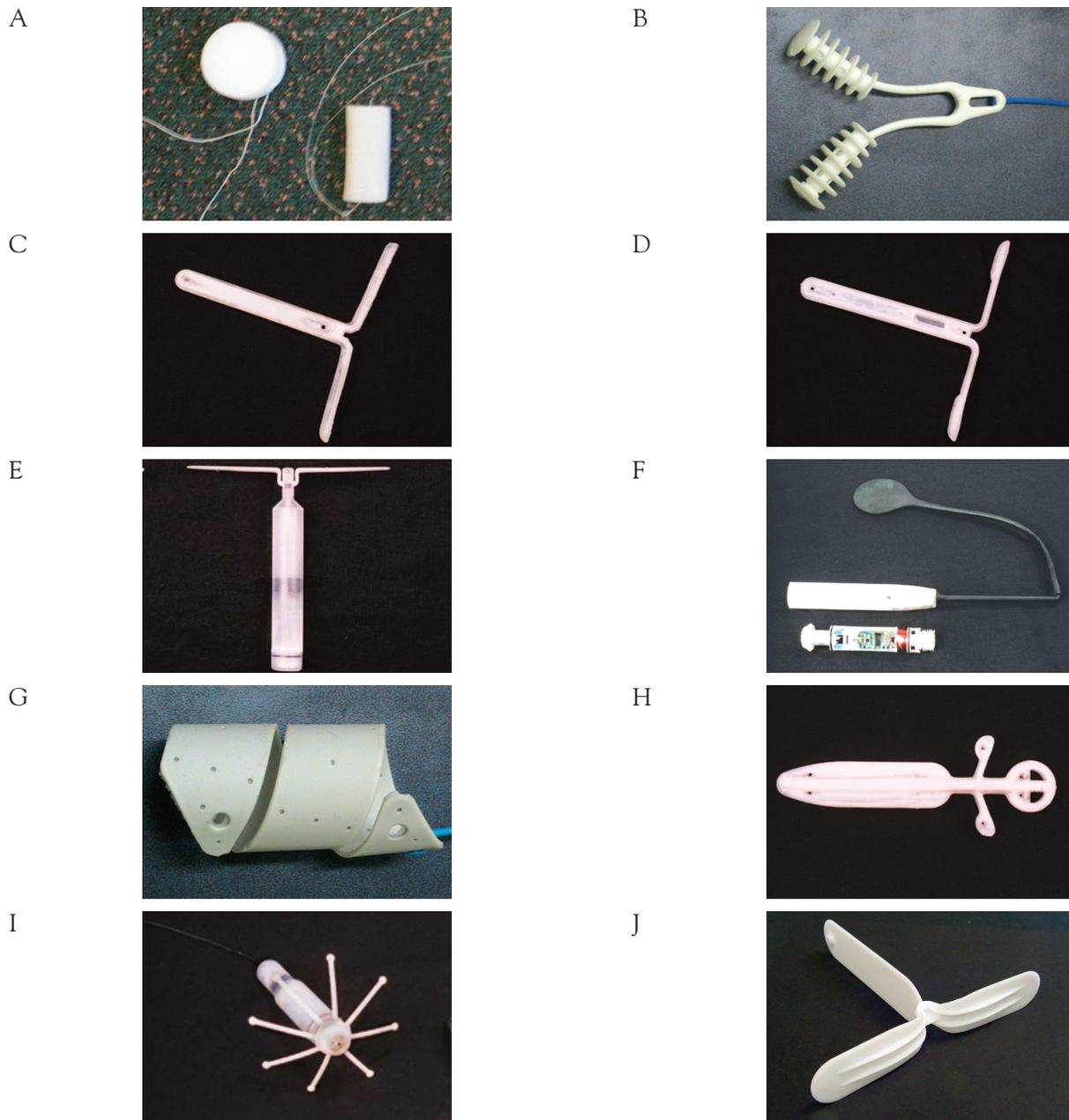
### **Controlled release intravaginal veterinary drug delivery**

The vagina of farmed animals such as cattle and sheep is an attractive site for drug delivery due to the ease with

which drug delivery systems can be administered and removed, its biological properties which are conducive to drug delivery, its ability to retain drug delivery systems for prolonged periods (weeks) and, although this route for drug delivery is sex specific, the uneven distribution of females within the farmed animal population, means that delivery systems developed for this route will serve the majority of the population owned by the farmer.<sup>5,6,10,5-32</sup> For drugs that are susceptible to gastrointestinal or hepatic metabolism, vaginal delivery may provide an alternative to that of the oral route of administration.

To date, commercially available intravaginal veterinary drug delivery systems have only been developed for the administration of synthetic and natural hormones such as progesterone, methyl acetoxy progesterone, fluorogestone acetate and estradiol benzoate.<sup>5,6,10,25-32</sup> However, progestins are among the most widely used reproductive drugs in veterinary medicine<sup>33</sup>, therefore the introduction of long acting intravaginal inserts containing hormones for the delivery of progestins has been welcomed by veterinarians and producers.

Historically intravaginal veterinary drug delivery systems have included polyurethane sponges containing synthetic progestins; silicone based inserts containing the naturally occurring hormone progesterone including: the PRID, CIDR-B, CIDR 1380 Cattle, CIDR Pig Inserts; electronically controlled inserts (Intelligent Breeding Device and EMIDD) capable of delivering multiple drugs at a predefined time, either pulsed or continuous fashion; and a biodegradable insert called the PCL Intravaginal Insert<sup>5,6,10,25-32</sup> (see Figure 1 for these various intravaginal inserts).



**Figure 1:** Range of commercially available intravaginal drug delivery technologies used in farmed animals. A = Sponges; B = CueMate; C = CIDR-B Cattle Insert; D = CIDR 1380 Cattle Insert; E = EMIDD electronic device; F = Smartt1 ; G = PRID; H = CIDR Pig Insert; I = Intelligent Breeding Device; J = PCL Intravaginal Insert.

In terms of use and performance all intravaginal inserts produce the required biological responses to control the estrous cycle of farmed animals, are safe to handle and are easily inserted and removed. Commercially available intravaginal veterinary inserts differ in shape. 'T' shaped intravaginal inserts include the CIDR-B (CIDR 1900 Cattle Insert) and its optimized version the CIDR 1380 Cattle Insert. Both comprise a nylon spine over which is injection molded a skin of silicone containing a homogenous dispersion of 10% w/w progesterone. Molding temperatures approaching 200°C are used to rapidly cure the silicone and consequently reduce cycle times thereby increasing the efficiency of the production process. The PCL Intravaginal Insert is also T shaped. This insert is a single piece injection moulded device comprising a homogenous dispersion of progesterone (10%w/w) throughout the biodegradable polymer polycaprolactone. It can be manufactured at temperatures of around 80°C. Its slow rate of degradation results in it retaining its physical properties during insertion, but completely degrades in the environment after it has been buried after use. The Intelligent Breeding Device has an 'umbrella' retention mechanism. This innovative insert uses electronics to control the delivery of progesterone from an intravaginal insert. It was the first intravaginal insert to be able to pulse dose compounds other than progesterone during insertion. The product underwent redevelopment and was re-introduced on the New Zealand market as the Smart1. The Smart1 has no wings to retain it inside the vagina of an animal during insertion, rather, it has a specially designed rubber retention mechanism that is glued to the back of the animal. A wishbone shaped intravaginal insert called the Cue-Mate is the only commercially available intravaginal insert to provide the opportunity to re-use the supporting spine upon which removable silicone fluted pods are fixed onto. The TRIU-B intravaginal insert has a unique cross-shaped structure which is purported to allow for a better anchorage, while minimizing device losses and local inflammatory reactions. Other shapes include the DIB-V Intravaginal

Insert which has a V-shape design and the PRID Delta which is a triangular in shape.

### **Veterinary long acting injections and implants**

A variety of long acting injectable and implant technologies have been investigated and commercialized for veterinary applications. Long acting injectable and implant formulations can be classified in the following categories: aqueous dispersions or solutions; oily injections; in-situ depots; microspheres; and implants.<sup>21,34-37</sup>

Long acting injectables and implants used in animal health must be formulated using biocompatible and safe excipients that have demonstrated safety and biocompatibility. Formulators usually choose excipients from the GRAS (generally recognized as safe) listing.

There are several farmed animal long acting injectable aqueous formulations available in the market.<sup>21,34-37</sup> In many cases the long acting nature of these injectable products are not a result of the formulation ingredients but rather through the innate properties of the drug.

A suspension or solution of active ingredient in oil and/or non-aqueous solvent system is a common formulation approach for long acting injectables. Many oils and non-aqueous solvents can be used including fixed oils (e.g., sesame oil, olive oil, castor oil), ethyl oleate, benzyl benzoate, isopropyl myristate, thin vegetable oil (fractionated coconut oil, polyethylene oleic triglycerides), and liquid polyethylene glycols (PEGs). When developing an oil based system, the ideal oil is stable and non-reactive to the drug, biocompatible, a good solvent or dispersing agent for the drug, and inert with respect to the primary packaging.

In situ forming depots are delivery systems that can easily be injected into farmed animals due to their relatively low viscosity liquids prior to injection, but following injection undergo a rapid change into a solid depot entrapping drug which is then slowly eluted over time. Many types of in situ forming systems have been

evaluated and reported for veterinary applications, including, those based on biodegradable polymer precipitation (e.g., Atrigel), sucrose acetate isobutyrate (SAIB) depot formation, and lipid-based liquid crystalline phase transitions.

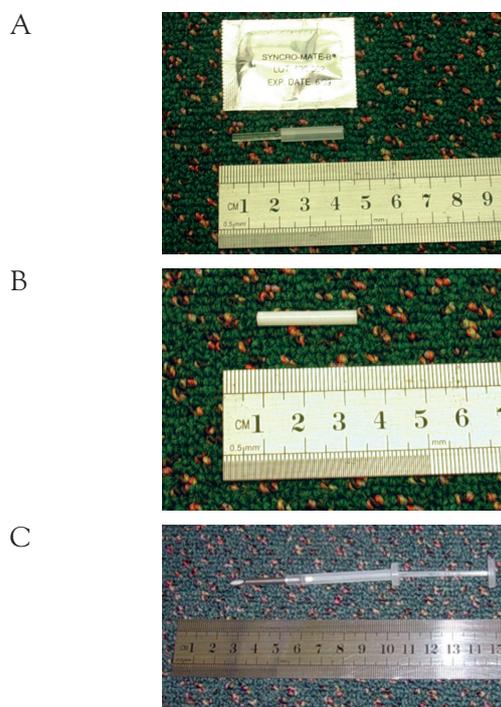
Microsphere based drug delivery systems have gained a lot of interest in the animal health industry, and some commercialized products have been marketed for farmed animal use. For example, the Smartshot injections contain Vitamin B12 encapsulated within PLGA microspheres suspended in peanut oil with the help of a suspending agent.

Implants have long been used in animal health, mainly for production enhancement in cattle. Since the 1950s, compressed tablet implants containing estrogenic anabolic steroids have been administered to improve feed conversion and the rate of weight gain in beef cattle. The implants are inserted under the skin of the back side of the ear where they slowly release the drug. The number and size of the implants vary among commercial products, as do the commercial devices for implantation. Examples include Compudose, Revalor, Synovex, Finaplix, and Ralgro implants. A range of implants are depicted in Figure 2.

### Veterinary vaccines

Excellent overviews of this topic have been published in the literature and the reader is referred to these publications.<sup>38-40</sup>

A major cost to farmers results from the morbidity and mortality caused by infectious diseases that can be prevented or improved by vaccination. However, vaccines need to be given at least twice and, depending on the duration of immunity required, booster doses need to be given at intervals as frequently as every 3 months (though more usually 12 months). The high costs associated with treating animals (herding, etc.,) results in the problem of lack of adherence to recommended protocols for vaccination by farmers. Thus farmed animals would benefit immensely from immunization with a single dose vaccine through the use of a



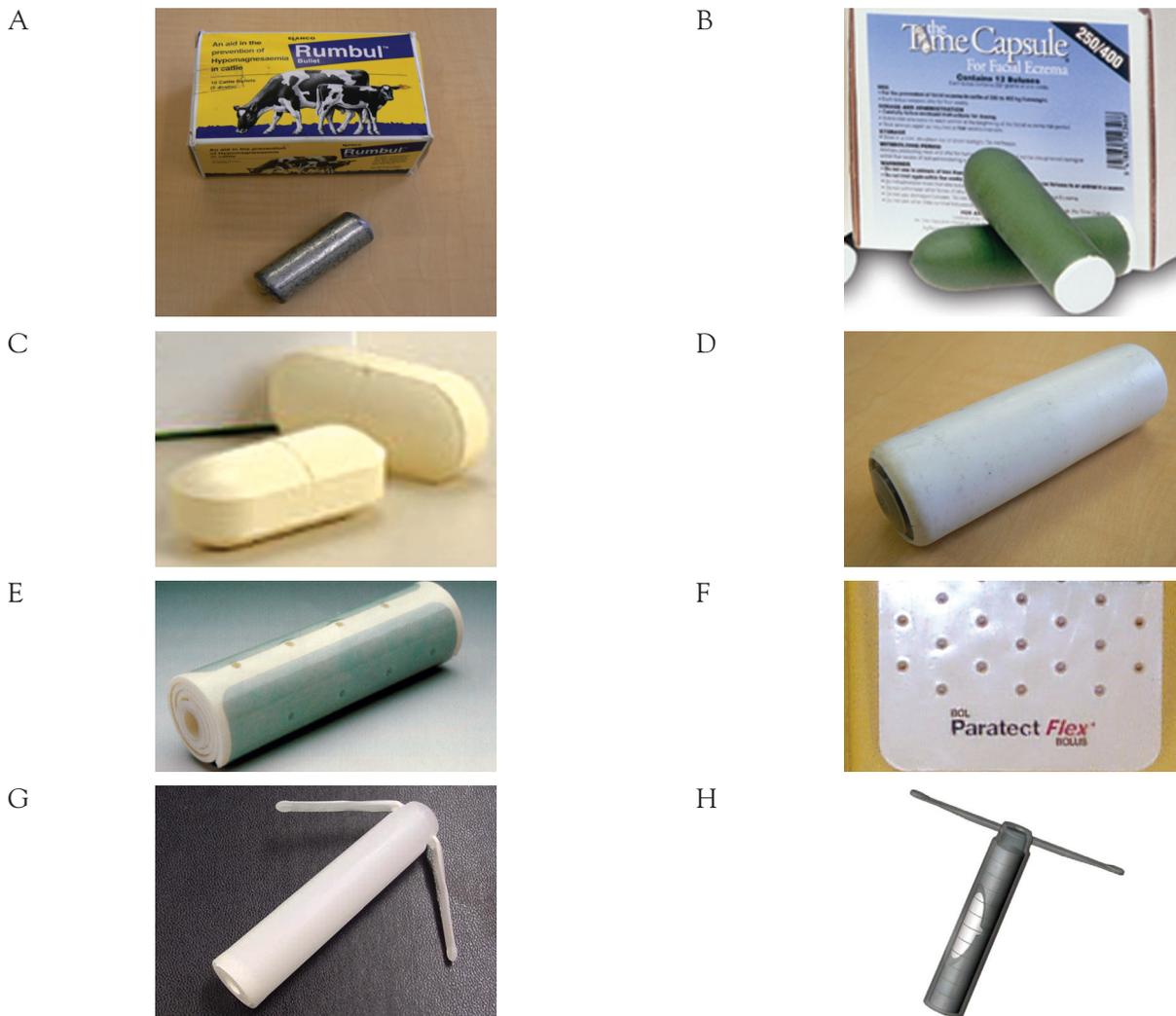
**Figure 2:** Range of commercially available implantable drug delivery technologies used in farmed animals. A = SynchroMate-B; B = Crestar Implant; C = Deslorelin Peptec Implant.

controlled release technology. However, the case of controlled release of veterinary vaccines is interesting since, unlike other preventative or therapeutic drugs which may be directed toward a single biological target, the aim is to present to the immune system a package consisting of an immunogen and immunostimulatory molecules in a particular manner that will result in germane and sustained immunity. This requires thoughtful presentation of antigen to the immune system in the context of appropriate immune signals. Many attempts have been made by formulation scientists to achieve this aim using a pulsed delivery system.<sup>41-43</sup> However, few controlled release vaccine formulations are available at this time despite the sophistication of the materials and devices used for controlled release of human and veterinary therapeutics.

**Long acting rumen drug delivery systems**

Because of the unique anatomy of the digestive system of ruminant animals (some pertinent features of which have been described earlier), long acting drug delivery technologies (or rumen boluses) can be designed to be retained in the rumen for prolonged periods permitting

drug release for durations of up to 6 months (or even longer). Indeed, since the beginning of the 1980's, many rumen boluses have been developed to prolong the release of antibiotics, anthelmintics, trace elements, growth promoting agents and minerals to the rumen of cattle and sheep.<sup>44,45</sup> Several rumen boluses are shown in Figure 3.



**Figure 3:** Range of commercially available ruminal drug delivery technologies used in farmed animals. A = Rumbul Bolus; B = TimeCapsule; C = Tablet rumen bolus; D = Ivomec SR Bolus; E = Paratect Flex Bolus (rolled up prior to administration); F = Paratect Flex Bolus (opened up after to administration) G = Captec Device; H = Housed Tablet Technology.

Rumen bolus can be manufactured by direct compression of solid metals or tablet excipients. Examples of the former include compressed boluses have been used to successfully supplement cattle and sheep with magnesium (e.g., Rumbul Bolus). Examples of the latter include formulations containing oxytetracycline, sulphadimidine or various trace elements. Alternatively rumen bolus can be manufactured by the process of extrusion. An example of this approach is the TimeCapsule which was invented in New Zealand and which slowly delivers zinc oxide for up to 6 weeks for the treatment of facial eczema. It principally comprises of zinc oxide together with a sufficient quantity of extrudable agents that enable the formulation to be extruded under high pressure into a rod. Following extrusion the rod is cut to length and then one end is shaped into a semi-circle. The zinc oxide core is then dipped into, and covered by, a waxy material. Drug release occurs via erosion from the exposed end of zinc oxide core. Zero order release is observed due to the presence of the waxy coating which prevents the zinc oxide core from eroding from the sides. When some of the zinc oxide core has eroded away, the waxy coating is no longer supported by the core and chips away, thereby ensuring a constant surface area of the core is exposed to the rumen environment.

The area of rumen bolus is characterised by the delivery technologies being very innovative of comprising a variety of shapes (Figure 3). For example, the Paratect Flex bolus comprises a flat trilaminar sheet manufactured using the polymer ethylene vinyl acetate containing morantel tartrate in the middle laminate layer. The flat sheet is rolled into a cylindrical shape prior to administration and retained in this configuration using a water soluble film. This allows the device to be administered via the back of the throat, however, following administration the film dissolves causing the flat sheet to unroll and be of a shape and dimension that prevents regurgitation by the animal. For economic reasons the Paratect Flex Bolus was withdrawn from the market. The Chronomintic is a matrix device with

the capacity to slowly release the anthelmintic drug levamisole. The matrix core is made up of particles of iron and levamisole hydrochloride. The core is bored in its center, the dimensions of which control the release of the drug. The external surface of the matrix core is covered with an impermeable polyurethane coating designed to prevent erosion of the core from the external surface. The Ivomec SR Bolus essentially comprises an osmotic pump that provides a sustained release of ivermectin in the animal at a uniform rate of approximately 12 mg/day for about 135 days. The Captec device comprises a hollow tube (capsule) that has a hole of fixed diameter at one end that acts as a delivery orifice and specially designed wings at the opposing end. Prior to administration the wings are held back along the capsule body using water soluble tape. Following administration the water soluble tape dissolves allowing the wings to spring open and form a shape that cannot be regurgitated by the animal. The plastic capsule is filled with tablets containing a complex formulation of drug and excipients. Before loading the tablets into the Captec device a long metal spring is placed in the closed end of the capsule. Drug release occurs following softening of the tablet formulation with rumen fluid. The softened formulation is then extruded out of the delivery orifice under pressure from the spring in a zero order fashion. The device has been used to deliver various anthelmintic compounds to sheep. Recently Wunderlich *et al.*<sup>46</sup> and Rathbone *et al.*<sup>47</sup> described a modification of the Captec device that was demonstrated to be more versatile in delivery duration, rate and drug type compared to the original Captec device. The workers demonstrated that the new rumen delivery technology could deliver drugs exhibiting a range of physicochemical properties from the water soluble, lipid soluble to completely insoluble into the rumen of cattle.<sup>46,47</sup> An alteration to the formulation excipient ratios, drug load (up to 70%w/w) or a change to the diameter of the delivery orifice (located in the side of the plastic capsule), or the number of delivery orifices could tailor *in vivo* release rates and/or delivery periods from a few days to up to 9 months.<sup>46,47</sup>

### Potential for academic institutions

The past decade has seen significant changes within the animal health industry through big pharma acquisitions and mergers. The high cost and risks associated with developing products for smaller, niche markets has caused major big pharma to be hesitant to conduct in-house product development for such products. This offers the opportunity for small companies and academic institutes to invest time and effort to develop such niche products and negotiate the provision of their specialized, patent protected technologies to big pharma. Big pharma interested in a technology would be willing to negotiate collaborative development deals; licensing of the technology either for clinical conditions, drug types or market regions; or outright purchase of the technology. In the ever growing competitive world of academia, this strategy can be adopted by academic institutes as a source of continuing research funding.

### Concluding remarks

The future growth of the farmed animal industry to meet human demand for food supply presents the opportunity for pharmaceutical intervention to assure high production rates though improved animal health, production and reproduction.

However, many challenges face the formulation scientist when developing a long acting veterinary drug delivery technology. Obstacles include the anatomy and physiology of the animals which varies greatly between species (and within the same species); different sizes and weights of animals; the need to devise some method of administering the product to the animal; the need to devise some method for retaining the product in the animal for the duration of release; and the fact that the meat, milk or eggs of these animals will be consumed and therefore the protection of the health of the consumer must be considered.

A long acting veterinary drug delivery system is of particular value in the farmed animal industry. This value has arisen because of the intensive methods of farming

animals such as cattle and sheep. This has resulted in the need for reducing the number of administrations of drugs to farmed animals since such animals are difficult to handle, time consuming to herd and treat, and get stressed when handled (which leads to a reduction in growth or production).

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