SCIENTEC RESEARCH PTY LTD
A.B.N. 32 058 744 371

Scientific and Technological Research Management, Consultancy and Best Practice

Our Ref: Sci1219z Technology Overview # 638a.wpd

10th May, 2004

Scientec Research Pty Ltd
71 Yarra Street,
WARRANDYTE, Vic., 3113.

COMMERCIAL-IN-CONFIDENCE

Re: Scientec's Controlled Release Technology

(File Note # 638)

DISCLAIMER

All information contained in this publication is as accurate and up-to-date as possible. Since Scientec Research Pty Ltd cannot anticipate or control the conditions under which this information may be used, each user should review the information in the specific context of the intended application.

Scientec Research will not be responsible for damages of any nature resulting from use or reliance upon the information. No expressed or implied warranties are given other than those implied mandatorily by Commonwealth, State or Territory legislation.

This document should not be reproduced except in its entirety.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

Ref: Sci1219z Technology Overview # 638a.wpd

10th May, 2004

SCIENTEC'S CONTROLLED (DELAYED) RELEASE DRUG DELIVERY TECHNOLOGY

Company Background

Scientec Research Pty Ltd is an Australian 'biotech' research and development company. Scientec has developed its own technology in drug delivery and controlled release. This technology is the product of an extensive in-house development program, augmented by strategic collaboration with selected University Departments and SME businesses within Australia.

Funding of Scientec's R&D programs has been through company cash flows supplemented with private borrowings and government grant support. Scientec's success in marketing its R&D services has resulted in projects with a number of leading Australian academic and industrial research groups, including:

- Schering Plough Limited (Drug Formulating);
- BioClip Pty Ltd (Drug Formulating and CRD development);
- Alpharma Pty Ltd (Drug Formulating and Down Stream Processing in Protein Refolding);
- Melbourne University, Centre for Animal Biotechnology (Formulation and Controlled Release Device development);
- Daratech Pty Ltd (Controlled Release Devices); and
- UNASCO Pty Ltd (Product Development/Analysis [R&D and QC]).

Scientec's core strength is its application of technical expertise and project management skills for the reduction to practice of laboratory protocols. In simple terms, taking R&D models and developing operational and pilot scale prototypes. The experience of Scientec's personnel extends through all stages of product and process development from research grant application and product development to full scale process implementation and marketing of technologies.

Expertise in non-core business areas is obtained on a contract/fee for service basis, and include Legal and Intellectual Property (Minter Ellison Lawyers), Accounting and Business Management (Armitage Downie), and Pharmaceutical Industry specific Process Engineering expertise (Pharmatec Pty Ltd and Pharmaction Pty Ltd).

The Technology

Scientec's core technology is centered on the Apparatus and Methods for manufacture of Controlled (delayed) Release Drug delivery (***"CRD"***) systems. Scientec's technology provides a simple and economical method for mass production of CRD's amenable to continuous automated clean room operation. In simple terms, Scientec's technology is a continuous manufacturing process for coating drugs. The process involves the extrusion of the coating structure onto the drug formulation using a machine the size of a desktop computer. The extrusion process first prepares the coating formulation and then coats the desired drug. Scientec has a semi automated production system capable of producing thousands of CRD's at a rate of 12 CRD's per minute.

Scientec's Apparatus and Methods are applicable to mass production of a variety of CRD's, providing a solution to problems which have previously remained unresolved. Devices that can be produced using the Scientec process include, (i) "macrocapsules", (ii) osmotic pump devices, (iii) microparticulates, and (iv) controlled release stents. The specific application for which the Apparatus is currently being engineered is the production of delayed/controlled release implants consisting of a 'drug core' formulation coated with (and sealed inside of) layers of a biodegradable coating, i.e. macrocapsules (generally cylindrical and up to or greater than 2.5 mm in diameter and 10 mm in length). The release of the encased 'drug core' arises subsequent to degradation of the coating. The release profile of the drug substance may be either pulsatile or sustained, depending upon the pharmacokinetic properties of the drug in the solid core.

In respect of the macrocapsule implants produced using Scientec's Apparatus and Method, the technology encompasses the following features:

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

- the implants may be as small as a 2 mm sphere, or up to (or greater than) 3 mm diameter x 10 mm length, carrying payloads of from 5 mg to 500 mg of drug, the upper limit being an estimated ethical one;
- solid-dose drug formulations are typically used, although fluid and granular based formulations can be accommodated;
- demonstrated delay of release times from nil to 650 days;
- reproducible batch to batch delays of release;
- limited variability of delay of release within a batch of devices;
- suitability for concurrent administration of multiple drugs, or multiple doses of a single drug, e.g. for the year round protection of cattle against worm infestation, or for single implant vaccines;
- the drug delivery profile following the delayed release is primarily determined by the characteristics of the 'drug core' and may be tailored to accommodate pulsatile and sustained delivery;
- suitable for use with FDA approved excipients;
- minimal site reactivity; and thus
- suitability for human and veterinary applications.

Additional Technical attributes and Performance details are provided in Attachment A.

Specific advantages of the Scientec Apparatus and Method for manufacture of CRD's include:

- continuous production method, yielding high product reliability (QC/QA and GMP conformity);
- solvent free processing, contributing to quality and reliability and avoiding any solvent residue; and
- cost effectiveness.

Intellectual Property

A description of Scientec's technology is contained in International Patent Application No. PCT/AU97/00872 entitled "Apparatus and Method for Coating a Material". Scientec is pursuing the grant of patents in all commercially relevant markets for the technology. Patent grant (or offer thereof) for Scientec's key technology has been received in Australia, New Zealand, India, Israel, the United States of America and South Africa. Patent grant is also being sought in Europe and Canada. Scientec anticipates achieving grant of patent in these territories. The timing of proceedings pertaining to examination and patent grant in the different territories is uncertain, however, it is anticipated that examination in Europe will follow during the next 12 - 24 months, and in Canada within the next 24 months.

Scientec currently retains 100% of its IP rights.

A variety of polymers have been used as coating materials, but the primary focus has been on the biodegradable polylactide polymer (pLa) used in resorbable sutures, which eventually breaks down to lactic acid. While this polymer is in the public domain, the formulation of the polymer to alter its degradation kinetics and make it melt extrudable are Trade Secrets.

Business Development Model

Scientec's objective is to become a leader in the field of Controlled Release Drug Delivery technologies through development and licensing Intellectual Property for CRD's (formulations, manufacturing processes and equipment) across the veterinary, human and agricultural industries.

Scientec's Business Objectives

The development and commercialization plan for Scientec includes the following short- and mid term objectives.

In the **short-term**, Scientec's commercialisation program anticipates:

1. Conduct of POC trials with potential Licensees using commercial 'drugs';
2. commissioning the design and manufacture of pilot scale Apparatus for device production; and
3. consolidation of Scientec's IP portfolio.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

In the **medium-term** Scientec anticipates being able to provide:

1. fully functional turn key operating units for installation in Licensee facilities (equipment to be sourced in Australia);
2. technology transfer, including training and supervision of Licensee staff in handling of the coating materials and Apparatus;
3. formulation of CR drugs for shelf life stability and reduced storage needs (e.g. on farm and in third world applications);
4. development support to Licensees (technology refinement) and automation (on line monitoring and process control); and
5. technology expansion to support the existing patent portfolio and to seek new patents to broaden the technology base.

Strategies to Drive Growth

The five areas where we believe new products and services can be generated are, from short term to long term:

- licensing of CRD coating technologies;
- contract drug formulating especially of solid dose (or other) formulations required for the CRD's;
- CRD product registration trials;
- CRD coating equipment, including improved equipment featuring highly automated process monitoring, reporting, quality control and packaging; and
- supply of coating formulations, which would be manufactured under licence by subcontractors.

Target Markets

The market for Scientec's technology includes all human and veterinary pharmaceutical companies and biological (vaccine) companies, as well as generic drug companies. The most attractive of these segments are proprietary products for:

- veterinary health regulatory approval times of 2 to 4 years for approved drugs or vaccines; and
- human health care the biggest and most profitable, but with longer approval times.

About Scientec's People, History and Current Situation

Scientec's core technology was developed and is wholly owned by Scientec Research Pty Ltd. Scientec's key personnel, Michael O'Donoghue and Jim Morris, have worked in the area of controlled drug release for over ten (10) years. During this time Scientec obtained government support through GIRD and R&D Start programs and has spent more than $A2.5 million to develop the technology.

Scientec has recently completed evaluation trials with one global and one Australian based pharmaceutical company, both of which operate in the human and veterinary markets.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

For further details, contact:

Dr. Michael O'Donoghue
Managing Director
Scientec Research Pty Ltd,
71 Yarra Street, WARRANDYTE 3113
Victoria, Australia

Phone [Mobile]:+61 (0)409 931 886
Facsimile: +61 (0)3 9844 2076
e mail: website@scientec-research.com

ATTACHMENT A

Technical Overview

Size of Delivery Device (Minimum and Maximum Dimensions From Technical and Biological Point of View)

A single 'device', as pictured (Figure 638.1), is approximately 3 mm in diameter and 10 mm long and contains a 35 mg drug core payload (ca. 2.3 mm in diameter and 5.0 mm long). This payload mass (volume) has been used for convenience of handling. It is anticipated that, for commercial applications, a 'device' accommodating a 35 mg drug core would have rounded ends, as illustrated schematically in Figure 638.2 and be approximately 2.0 mm in diameter and 5.0 mm long.

Figure 638.1: Photograph of a CR 'devices' as currently produced

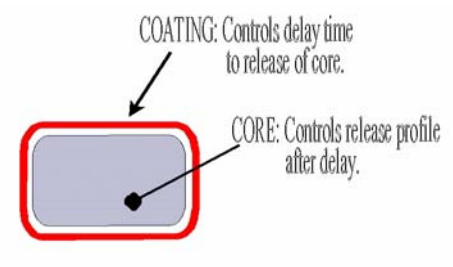

Figure 638.2: Schematic of CR 'device' following further process development

The maximum 'device' size would be governed by payload requirements and ethical considerations. To date the largest 'device' we have produced for testing *in vivo* (cattle) contained a 500 µl fluid payload (a 'device' approximately 6 mm in diameter and 25 mm in length).

One of the independent POC trials (below) entailed administration of four (4) 'devices' (plus a 'priming' dose), each of the 'devices' being ca. 4 mm in diameter and 15 mm long, and each 'device' carrying a 200 mg 'payload'.

Table 638.1 presents data pertaining to dose 'mass' and 'device' volume for tableted (cylindrical) solid dose drug cores.

Drug-core 'mass' **(mg)**	**'CRD' volume (mm^3)** **(l x ι mm)**
5	7 (1.4 x 3)
35	50 (2.2 x 5)
50	70 (2.2 x 7)
100	140 (2.7 x 9)
250	360 (3.7 x 11)
500	715 (4.2 x 16)
1000	1430 (5.0 x 21)

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

Drug Delivery: Pulsed and/or Continuous Release

The means by which **delay of release** is achieved is independent of the 'drug dose' formulation (the 'core' of the 'device' in Figure 638.2). If the 'drug-dose' contains hydrophilic materials, it will wet and disperse/dissolve rapidly, thus providing a 'pulsatile' delivery profile. On the other hand, if the 'drug-dose' contains hydrophobic materials it will wet only slowly and slough off (erode) at a rate dependent (in general terms) on the partition coefficient, thus providing a 'sustained' release/delivery profile. Flexibility in the release profiles achievable is because of the **independence** of the payload from the mechanism for control of (delay of) release of the dose(s).

For the POC studies (internal and independent), we have worked with three 'drug' types and with a primary focus on pulsatile release. We have, however, been involved in work targeting sustained delivery subsequent to a delay of release.

Specifically, the **pulsatile delivery** programs have entailed work with:

1) brilliant blue and methylene blue, water soluble 'pharmaceuticals' which are useful for studies of release *in vitro* and *in vivo* (respectively);
2) vaccine antigens, through comparing the effectiveness of the immune response obtained from Controlled Release delivery of antigenic materials (results comparable to "standard" immunisation protocols); and
3) the high potency anthelmintic Ivermectin.

The sustained release studies have mostly been with the high potency anthelmintic Ivermectin. However, we have been collaborating in development of sustained release 'hormone devices' for application in sheep and pigs using the combined effects from 'drug formulating' and the Controlled Release 'devices' to affect alterations to the hormones pharmaco kinetic profiles.

Independent Proof of Concept Studies in Domestic Species

Biodegradable Vaccine Implant Trials

POC Trial A: A 21 day Controlled Release Vaccine Formulation in Sheep

Figures 638.3, 4 & 5 represent data from an independent POC evaluation of the Scientec technology. The graphical representations are the mean antibody titers [Ab] against time for a 5-component commercial antigen mixture given as (i) the conventional 2 dose liquid formulation at days 0 and 21 (Figure 638.3), (ii) a 'naked' solid dose together with a non irradiated 21 day CRD, also at day 0 (Figure 638.4) and (iii) a 'naked' solid dose together with an irradiated 21 day CRD at day 0 (Figure 638.5). The study was conducted in sheep.

The data show bioavailability from both the 'naked' and CRD formulations, with responses to a number of the antigens (particularly antigen 2) from the 'naked' plus CRD formulations being comparable to or greater than those obtained from the conventional liquid vaccine Control group. Interestingly antigen 2 also appeared very sensitive to sterilizing irradiation. Parallel studies in mice corroborated these data.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

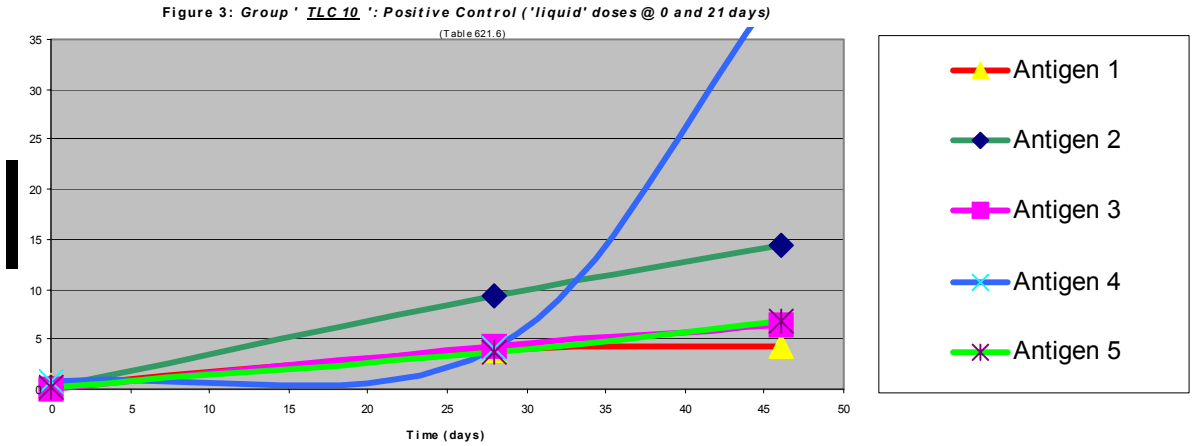

Figure 638.3: Antibody responses of sheep vaccinated with the 'Control' liquid vaccine at days 0 and 21

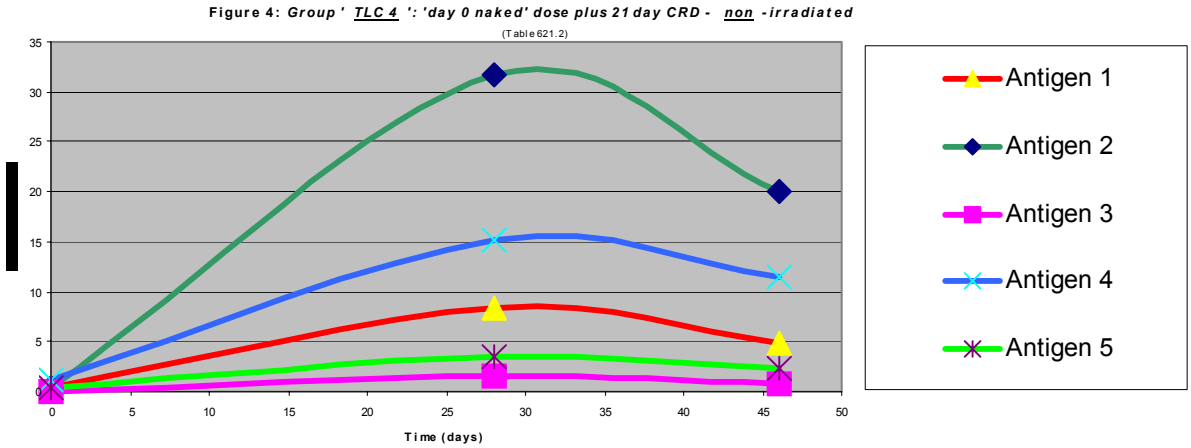

Figure 638.4: Antibody response of sheep vaccinated with a 'naked' solid dose plus a day 21 CRD, both at day 0. The CRD formulation **was not** irradiated prior to implantation.

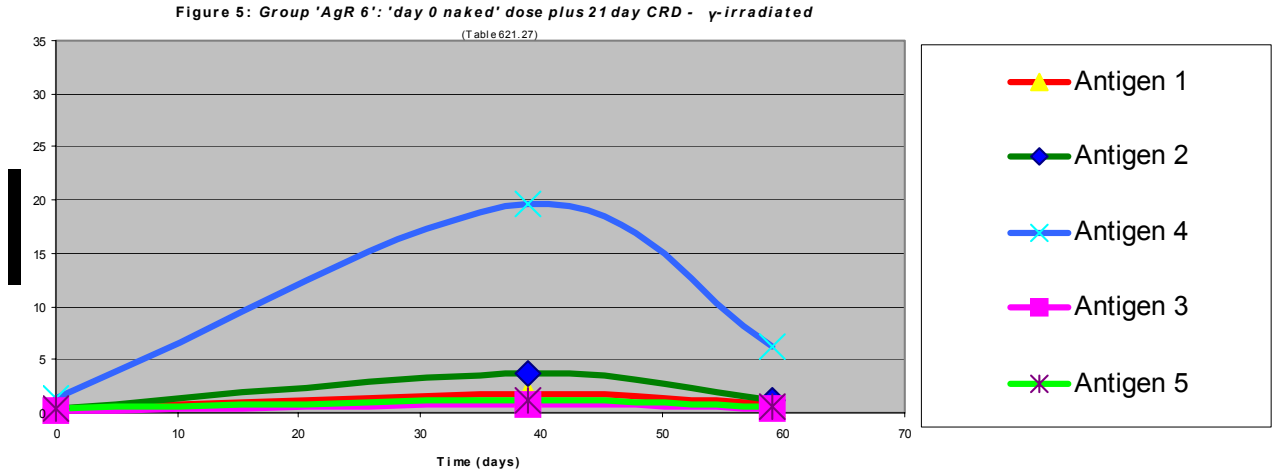

Figure 638.5: Antibody response of sheep vaccinated with a 'naked' solid dose plus a day 21 CRD, both at day 0. The CRD formulation **was** irradiated prior to implantation.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

POC Trial B: A 25 and 100 day Controlled Release Vaccine study in Cattle

Figures 638.6 & 7 represent data from a second independent POC evaluation of the Scientec technology. In this cattle study an anti-metabolite antigen formulation was administered. Figure 638.6 shows the mean anti-metabolite antibody response over time for the Control 2-dose liquid formulation and the Experimental group that received a priming 'naked' solid dose of vaccine at day 0, together with a dose of the solid antigen in a 25-day and a 100-day CRD. While the CRD vaccine did not reach the peak titres of the 2-dose liquid formulation, the response persisted at significant titres for a similar period of time.

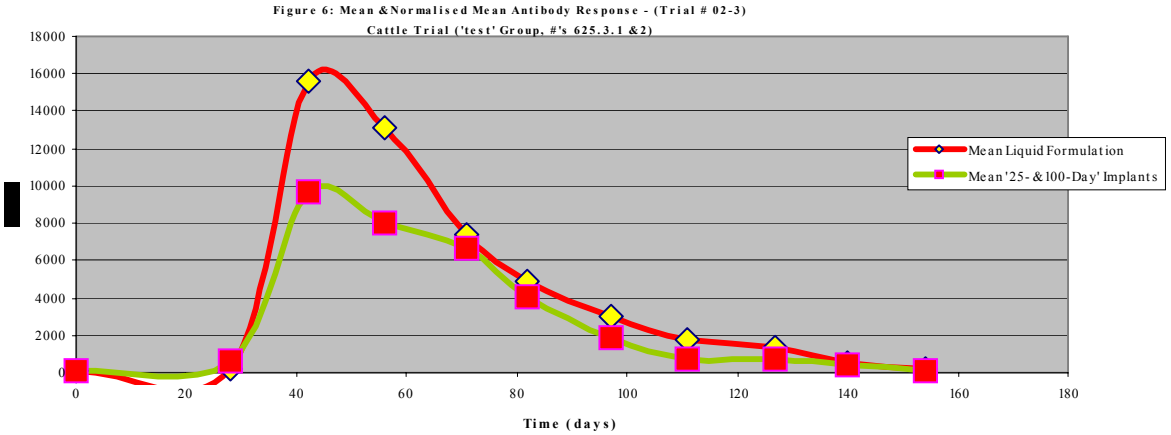

Figure 638.6: Mean anti-metabolite antibody responses against time of Control cattle given 2 liquid doses of vaccine on days 0, 25 and 100, compared to the Test group that received 3 doses of solid vaccine, one naked, one in a day 25 CRD and one in a day 100 CRD, all on day 0.

To evaluate the biological significance of the anti metabolite responses, the plasma levels of metabolite was measured in both groups. The geometric mean metabolite concentration was suppressed in both the Control and Test groups for a similar period of time (Figure 638.7). The data show bioavailability from the CR formulations, with the responses to the antigens from the CR formulations being comparable (not significantly different) to those obtained from the Positive Controls. Parallel studies in mice corroborated these data.

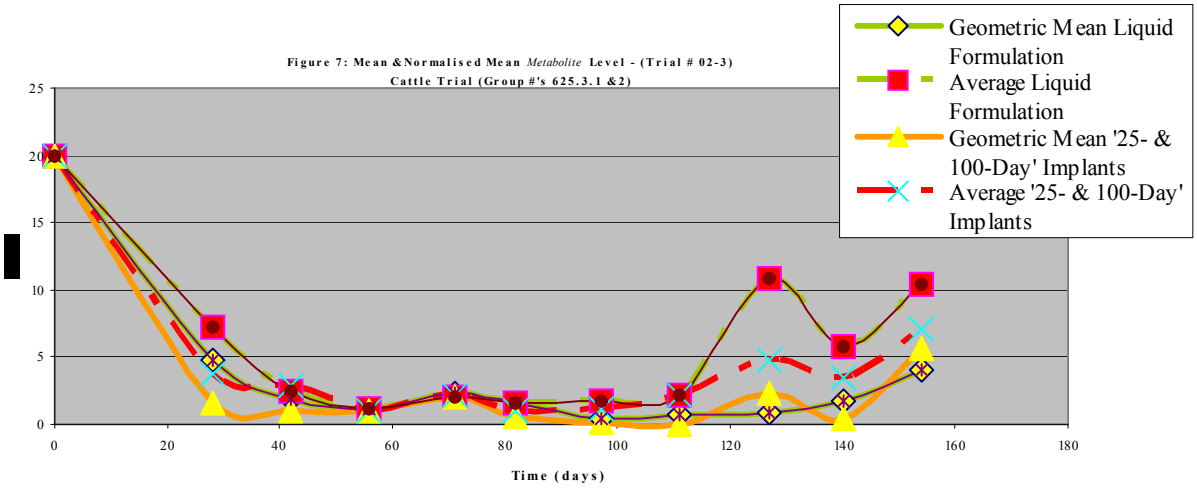

Figure 638.7: Mean Metabolite levels over time of cattle receiving 3 doses of the liquid formulation 'Control vaccine' and the 'Test' cattle that received day 25 and day 100 CRD vaccine together with a 'naked' solid dose of vaccine at day 0.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

Biodegradable Anthelmintic Delivery Trial

POC Trial C: A 42 and 150 day Controlled Release Anthelmintic in Sheep

A third independent POC evaluation of the Scientec technology is a sheep trial with three doses of an anthelmintic formulation targeting delay of release times of 0, 42 and 150 days. Figure 638.8 shows the plasma concentration of anthelmintic over time in the Control group receiving conventional liquid doses at days 0, 42 and 150, while Figure 638.9 shows the plasma levels of anthelmintic in sheep implanted on day 0 with the 42-day and 150-day CRD's together with a 'naked' solid dose of anthelmintic. The data show bioavailability from the 'naked' solid dose (day 0) and from both of the CRD formulations (i.e. at days 42 and 150). Although the peak plasma levels of anthelmintic were not as high as those in sheep receiving the liquid formulation, the shoulders of the peaks were broader and provided sustained plasma levels of anthelmintic. The CRD formulation suppressed faecal egg counts in the treated sheep, as compared to untreated sheep, for over 200 days.

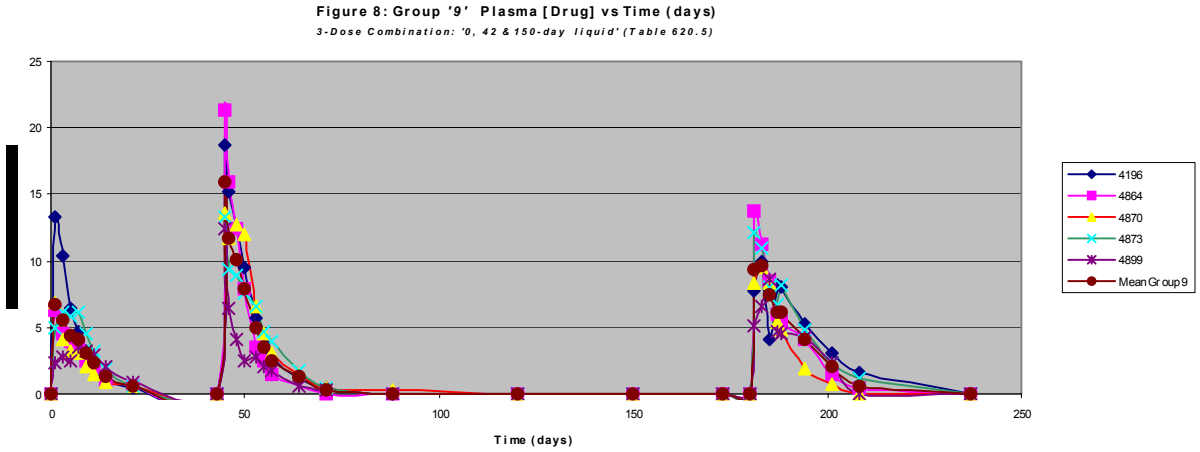

Figure 638.8: Anthelmintic levels in Control sheep receiving liquid doses of drug at days 0, 42 and 150.

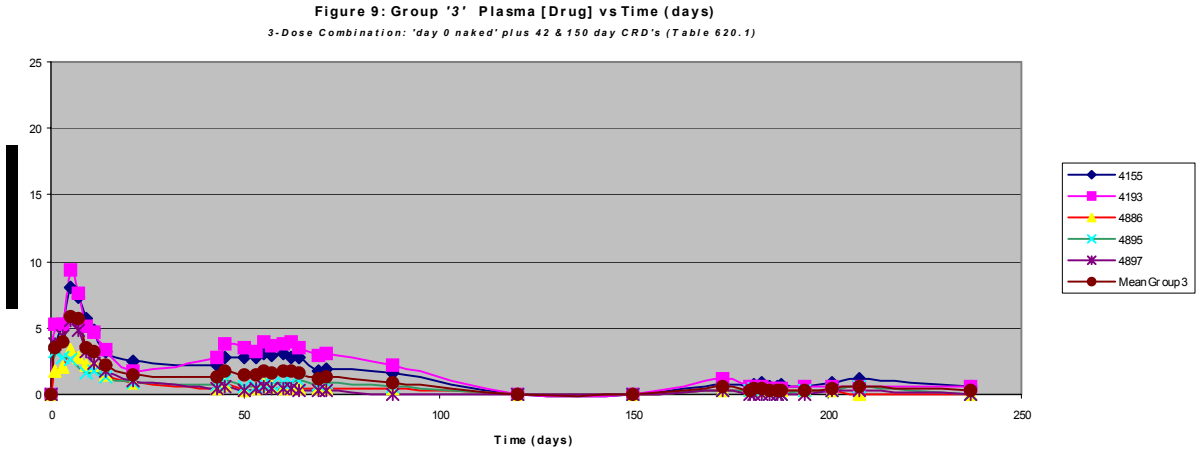

Figure 638.9: Anthelmintic levels in Test sheep receiving a 'naked' solid-dose and 42 & 150 day CRD's at day 0.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

Repeatability and Reproducibility

We have detailed in house reports covering the majority of *in vitro* and *in vivo* studies conducted to date with brilliant blue and methylene blue (sentinel monitoring), vaccine antigens, and the anthelmintic Ivermectin. Detailed Reports can be made available as required.

The delay of release times *in vivo* **and** *in vitro* have exhibited standard deviations of time of release about the mean release time of generally less than 10%, even at 600 days. Many of the *in vitro* studies have exhibited a standard deviation of release time of less than 5% of the mean release time. The 'consistency' of the standard deviation at the distinctly different delay of release times is believed to be because of the consistency of the mechanism whereby the coating formulation controls the delay time to release.

In addition to Scientec's own 'in house' data, we are able to cite a considerable body of relevant data from other independent studies (ca. 10,000 data points) using a comparable implant structure, but manufactured using a quite different approach. Scientec personnel were directly involved in the technology development program which generated these data.

A summary of these data are presented in Figures 638.10 & 11 and in Table 638.2. The data in Figure 638.10 shows the *in vitro* release of device targeted at 60, 95 or 110 day delayed release, while Figure 638.11 shows the *in vitro* release from 4 different batches of devices targeting 95 days release. Table 638.2 provides a comparison of cross-'species' data from the groups of CRD's represented in Figure 638.11. Overall these studies demonstrate:

- good repeatability and reproducibility; and
- comparable 'performance' across species and 'test' system (*in vitro* and *in vivo*).

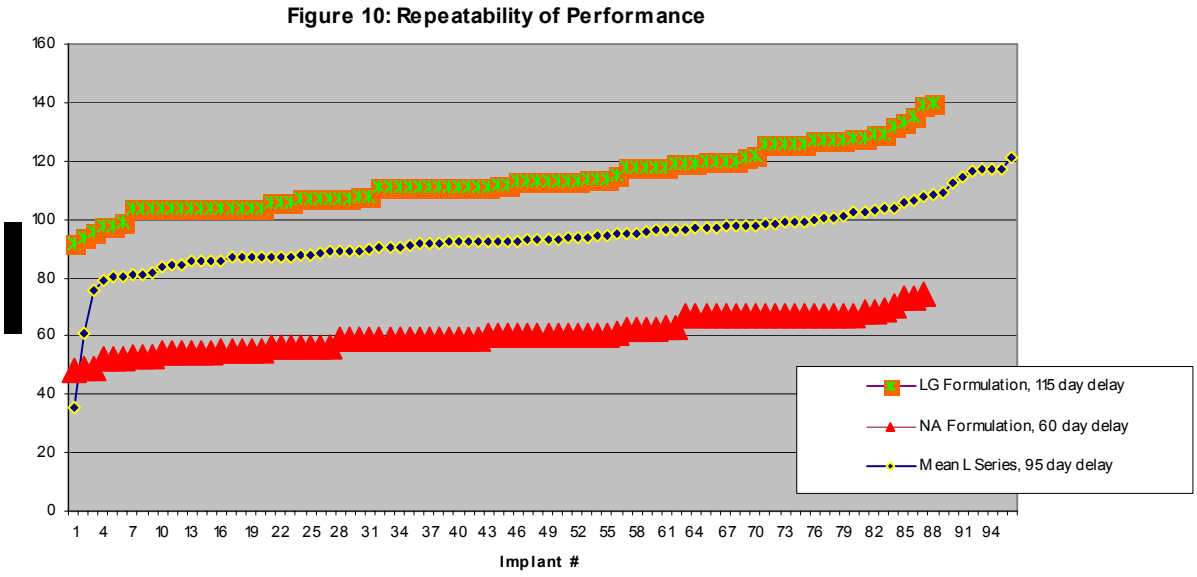

Figure 638.10: Repeatability Data.
In vitro release of marker drug from 90 CRD targeted at either 60, 95 or 110 days delayed release.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

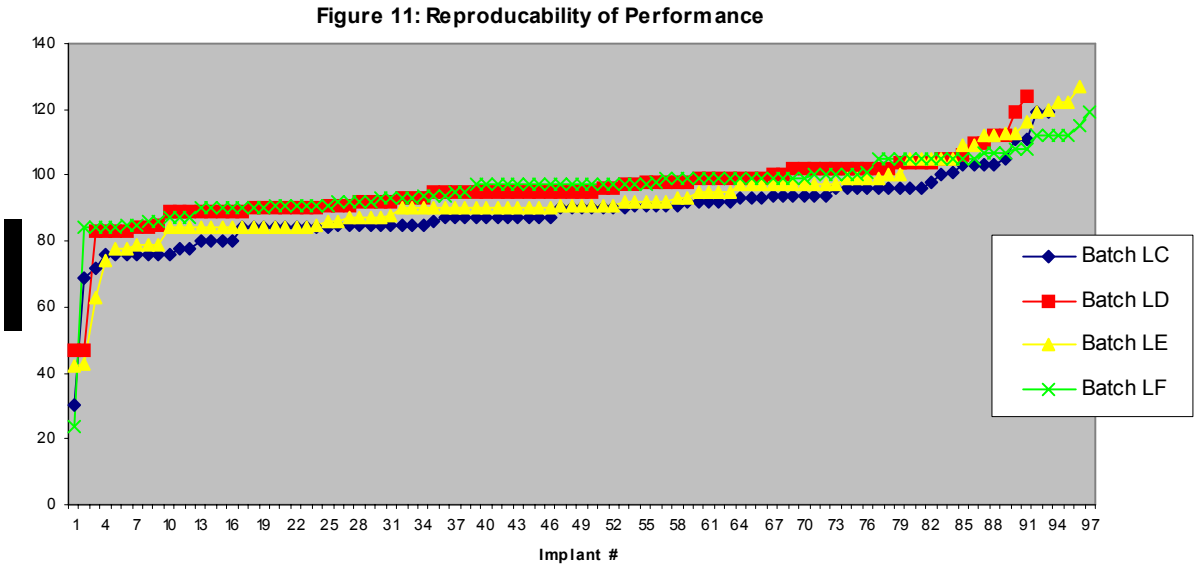

Figure 638.11: Reproducibility Data
In vitro release of marker drug by 4 different batched of CRDs, all targeting 95 days delayed release.

Table 638.2: Release Data from 5 Experimental Groups

Experimental Code	*in vitro*		Mice		Sheep	
	Sample Population	Sample Mean (Stdevp)	Sample Population	Sample Mean (Stdevp)	Sample Population	Sample Mean (Stdevp)
LC	10	92 (11)	100	89 (11)	20	96 (7)
LD	10	94 (10)	100	95 (10)	20	98 (7)
LE	10	85 (2)	100	93 (13)	20	98 (8)
LF	10	97 (4)	100	96 (10)	20	100 (5)
LG	10	84 (5)	100	114 (10)	20	100 (6)

Minimum and Maximum Delay of Release

The minimum delay of release which can be achieved with the base 'formulations' we currently use is 15 days. The lower limit is because coating formulations which give delay times of less than 15 days lack structural integrity. That is, they are 'brittle' and hence not commercially viable. We anticipate being able to develop 'structurally sound' formulations with delay of release times of less than 15 days if required, given sufficient resources for the formulating program.

The maximum delay of release we have achieved is approximately 600 days. However, the majority of our work has been focused on delays between 15 and 120 days. As such, we have achieved delay of release times of approximately:

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au

15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 100 and 120 days.

We also have (limited) data exemplifying delay of release times in the range 150, 180, 220 and 600 days. The limited data and range of 'extended' delay times achieved is due to the turnaround time on such experiments, and our resource limitations.

Our know how provides us with sufficient understanding of the materials to enable us to formulate delay times other than those listed. By way of example, shifting the delay from 120 days to 110 days using processing parameters and/or addition of excipients.

Address for Correspondence: Scientec Research Pty Ltd, 71 Yarra Street, WARRANDYTE 3113, Victoria, Australia.
Phone [Mobile]: +61 (0)409 931 886; Facsimile: +61 (0)3 9844 2076; e-mail: scientec@labyrinth.net.au