Market Review

Development Of A Combination Salmonella/Campylobacter Vaccine

Primary Industry Council/Kellogg
Rural Leadership Programme
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RESEARCH • PERFORMANCE • INTEGRITY

Salmonella / Campylobacter Sheep Vaccine Market Review

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Executive Summary

The Problem

Serotypes of *Salmonella* are the cause of two problems in the New Zealand sheep population. The first is enteric salmonellosis causing scours, which is widespread in the North Island and in the South Island effects Canterbury, Otago and Southland.
The Second is *Salmonella brandenburg* which causes abortions and ewe deaths. This has been seen only in Canterbury, Southland and Otago.
The enteric form of the disease had been acknowledged for many years, however S. *brandenburg* was first isolated in Mid Canterbury in 1996. The disease then extended into Southland and Otago in the late 1990's and had a catastrophic effect on ewe flocks around Southland in 1999 resulting in significant loss of productivity through loss of potential lambs from abortions and the loss of breeding ewes
This disease is also a zoonosis and there has been a continuing increase in the number of human cases reported over the last 10 years.

Over the past 5 years there have been a large number of farmers that have requested a combination vaccine for the sheep. The idea of a combined campylobacter and salmonella vaccine is one that has been often spoken about by farmers, vets and industry. The majority of sheep farmers are tired of the number of vaccinations that they have to give their sheep.

The Potential Solution

The best possible solution to this issue would be the development of a combination vaccine incorporating Campyvax4® and four salmonella antigens *(S. hindmarsh* S.*typhimurium, S. bovis-morbificans and S. brandenburg).* However if we are not successful in any part of developing a combo vaccine then we have got the fall back of manufacturing a stand alone Salmonella vaccine.

Farmers would benefit from having two vaccines in one and it is hoped that we would get a vaccine that would give better results than that of Salvexin®+B for *S. brandenburg.*

We would also need a stand alone salmonella booster vaccine for *S. brandenburg* that would be administered as a third vaccination in the first year and an annual booster thereafter for Southland, Otago and parts of Canterbury. This vaccine would most likely be administered at day 90 of gestation which should tie in with pregnancy scanning.

Competitors

Salvexin+B® (Schering Plough Animal Health) is the current vaccine used for Salmonella in sheep. This vaccine contains inactivated *S. hindmarsh S.typhimurium, S. bovis-morbificans and S. brandenburg* utilising alum as the adjuvant and 0.5% w/v phenol as preservative. This vaccine has shown to have a good level of efficacy against the enteric form of this disease, however it has been reported to show a lack of efficacy against *S.brandenburg* together with reported injection site reactions or endotoxemia

There is a low probability of further competition due to the limited size of the market.

The Market

The combination vaccine would be utilised in the areas that currently have problems with salmonella both enteric and abortion. These include Gisborne, Hawkes Bay, Wairarapa, Manawatu, Canterbury, Otago, and Southland.

The booster vaccine would be limited to the areas of New Zealand where suffer from S. *brandenburg*. This includes; parts of Canterbury, Otago and Southland.

The total market for a combination and/or a booster vaccine consists of 6,361,194 replacement ewes per year.

The market for the booster vaccine consists of 3,702,363 replacement ewes that are part of the national replacements figure above.

Introduction

For many years now New Zealand Sheep farmers have been asking the question "Why are there not more combination vaccines available". There are good examples of combination vaccines in the dairy industry but not so for the sheep industry. In NZ there are vaccines such as clostidial 5 in 1 and 10 in 1 vaccines available, these vaccines deal with the family of clostridial bacteria.

For the purpose of this market review the term combination vaccine is the blending of two different bacteria – in this case *Salmonella* and *Campylobacter* strains. In investigating the issues it is well understood that both Salmonella and Campylobacter play an important role in limiting production on NZ sheep farms.

In 2005 Intervet NZ launched Campyvax4® - a vaccine containing Campylobacter *fetus* subsp. *fetus* and *jejuni*. There is currently one other Campylobacter vaccine available. At present there is only one vaccine in NZ available for protection against Salmonella in sheep which is available from Schering Plough Animal Health.

The intention of this report is to investigate the potential for a combination vaccine containing Campyvax4® and adding four strains of Salmonella. In this report there are a number of areas that will be looked into including an overview of how *Salmonella* effects the NZ sheep population, the market and statistics, competitors, science/technology, product development, IP and how this new vaccine would be produced and marketed.

The focus will be predominantly on Salmonella and the market surrounding a combination vaccine. The options available if the ideal combination vaccine is not possible will also be discussed.

There are many ways in which this project can be viewed with a number of different options. This report focuses on the market potential and the possibilities available. For that reason it does not include financial information. The contents of this report will be added to the financial information at a later date to make up the entire business case for the project.

Market Proposition

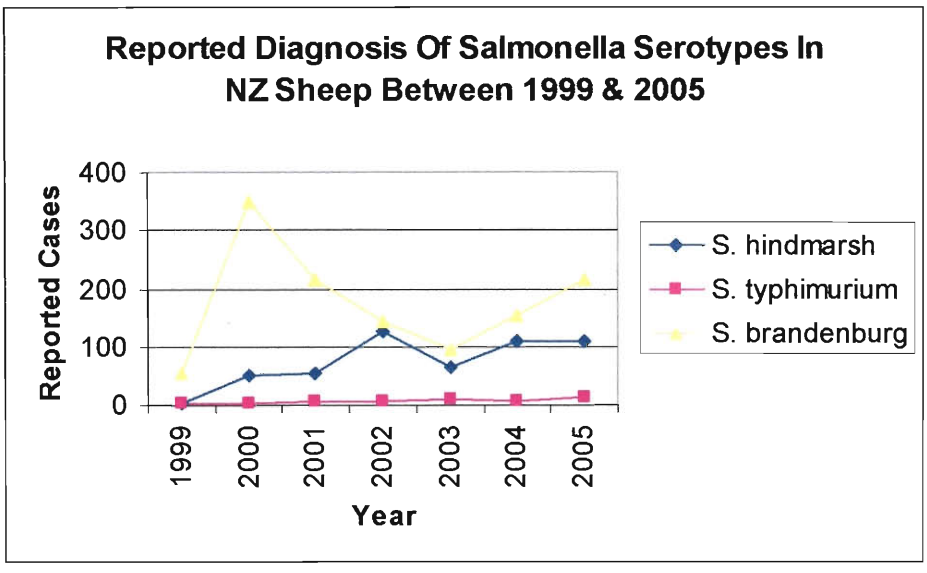
Salmonella found in the New Zealand Sheep population can be split into two separate forms; firstly enteric salmonella which is characterised by profuse diarrhoea and commonly death. This form of Salmonella is caused by *Salmonella enterica* subsp. *enterica Serovar* hindmarsh, *Salmonella enterica* subsp. *enterica Serovar*. typhimurium and *Salmonella enterica* subsp. *enterica Serovar* bovis-morbificans. The other type of Salmonella causes abortion – namely *Salmonella enterica* subsp. *enterica Serovar* brandenburg.

Geographical Spread

Salmonella causing enteric disease was first reported in New Zealand in 1949 and during the 1950's the disease was largely confined to Hawkes Bay, Manawatu and the Wairarapa regions. However, since that time salmonellosis has become wide spread throughout most farming regions (Bruere,West. 1993)

In 1996 *S.* brandenburg – a serotype that had previously only caused sporadic disease in many different species, was isolated from aborting and dying ewes in Mid Canterbury (Bruere,Ridler & West. 2002). Sine then this form of the disease has been recognised in South Canterbury, South and West Otago and in Southland. There have also been a couple of cases reported in North Canterbury.

Graph 1:



Source: ESR – July 2006

Since the large outbreak of *S.brandenberg* in 2000, the number of reported cases has declined. However in 2004 and 2005 there has been a sharp rise in cases reported.
S hindmarsh has been on a steady increase over the six year period. (Graph 1). It is interesting to note that for the two year period from 2002 – 2004 the trend of *S brandenburg* and *S hindmarsh* cases reported were similar.

From the information reported this disease, causing both abortions and enteric disease is still making its presence felt. The levels of *S. brandenburg* that have been reported in the last couple of years is of particular concern given that the onset of vaccination in 2000 was showing promising signs of gaining some control in the lower regions of South Island.

Pathogenesis

New Zealand is the only country in the world that has reported *S.brandenberg* as a cause of abortions. While *S hindmarsh, S typhimurium* and *S brandenburg* can all cause deaths in sheep, *S brandenburg* is the only serotype currently identified in New Zealand that causes abortion.

Enteric

During an outbreak of salmonellosis, there is a rapid transfer of infection from infected to non-infected animals. However there is evidence to suggest that under stress, the resistance of the carrier or infected animal is reduced, leading to a rapid multiplication of the bacteria in the rumen and possibly the intestine. This is followed by a bacterial invasion and the systemic spread of the disease. Some animals survive this stage of the disease but localisation of the organism occurs in the mesenteric lymph nodes, liver, spleen and in particular the gall bladder. These animals become chronic carriers of the disease and discharge organisms intermittently into the faeces and occasionally into milk.

In the majority of epidemics, some sheep are usually found dead and concurrently several ill or dying sheep may be found, usually near a water source. Sheep with clinical enteric salmonella are acutely ill. They have elevated temperature, are dull, disinclined to move and have severe and profuse diarrhoea. The faeces are fluid and contain a large amount of mucous and occasionally flecks of blood. The faeces are putrid smelling , khaki coloured and usually adhere to the wool of the crutch and hind limbs. In per acute cases death may occur before the diarrhoea has developed. Less severely affected sheep may die after a sickness lasting from 12 -24hrs. During the terminal stages of the disease, sheep become severely dehydrated and although some sheep may recover, the convalescent period is usually protracted.

Since it was first reported in New Zealand enteric salmonellosis of sheep has been recognised as having a seasonal pattern of occurrence between December and June.

It is generally accepted that salmonellosis is a disease in which carrier animals occur commonly but clinical disease only occurs as a result of some stress factors. The following have been cited as predisposing factors.

- Sudden changes in nutrition
- Holding sheep in yards for long periods
- Transport overlong distances (on foot and by truck)
- Heavy stocking rates

These management procedures can lead to rapid transfer of infection from one sheep to another via pasture, particularly around drinking areas. (Bruere, West. 1993)

Abortion

Ewes are infected by direct contact with aborted foetuses/placenta or by ingestion of contaminated feed. The organism probably has an environmental survival of four or more months and the sheep that survive become intestinal carriers for up to six months. The carrier sheep are likely to be important for the introduction of infection into a naïve flock. Black backed gulls (*Larus dominicanus)* have been shown to carry large numbers of organisms, with up to 25 million organisms per gram of intestinal contents reported. Excretion of the organism in the faeces of black backed gulls may enable introduction onto a new property. Farmers and vehicles are also likely to be important vectors in the transmission of disease. The *S. brandenburg* isolate has also been isolated from sheep yard dust.

Both two tooth and mixed age ewes are affected but the majority of abortions are in multiple bearing ewes. Ewes in late pregnancy become dull and fevered and abort putrid late term lambs that have been dead for at least one day. Around half the aborting ewes subsequently develop severe necrotising metritis and die. Occasionally ewes may develop severe diarrhoea before death. Some ewes have only a short-term dullness and there lambs are born dead, small or weak. Combined farm data shows that on average 3-4% of the flock abort (range: 0.2-25%) over an average period of 30 days (range: 7-75 days). Without treatment 30 – 50% of aborting ewes subsequently die. (Bruere, Ridler West. 2002)

Current Situation

A tri-valiant vaccine (Salvexin®; Schering Plough Animal Health) containing S. *hindmarsh*, *S. typhimurium* and *S. bovis-morbificans* had been available for some time prior to the large outbreak of *S. brandenburg* in 2000. This vaccine had been used extensively with good results for the enteric form of this disease and was therefore initially used to try and reduce or control the effects of *S. brandenburg* as it was thought that there would be some degree of cross protection with *S.typhimurium* and also because it was the only vaccine on the market. This was not to be the case and *S. brandenburg* was added to the vaccine in 2000 to become Salvexin +B® (Schering Animal Health).

Since its launch Salvexin+B has been reported by farmers and vets to have only limited efficacy against S. *brandenburg.* This sentiment has been backed up by a survey of both vets and farmers in mid 2006. Appendix 1 Nick Gorman, Intervet NZ

The following are quotes from three farmers that were surveyed:

" I have stopped using salmonella abortion vaccine four years ago, as the cost and workload was too high when measured against the level of protection." LT Lindsay – **Balclutha**

"I have in the past used salmonella vaccine but I still had salmonella abortions, so I no longer use any vaccine." Cliff Cochran – **Otautau**

"I don't know it is of much use against S. *brandenburg* abortions." Shaun Brankin – **Drummond.**

Schering Plough's literature claims that Salvexin®+B will reduce the incidence of abortion in two tooth ewes by only 59%. This vaccine also has some degree of safety issues, probably due to endotoxemia, caused by endotoxin in the vaccine.

The following quote, taken from an Otautau Vets Ltd Newsletter in January 2006 following a survey conducted by John Hicks.
" This survey has done nothing to change our opinion that for most farmers vaccinating with Salvexin+B® is expensive insurance with no guarantee of a payout. If you have not had S. *brandenburg* before we see little justification for recommending it" "I will end this section by quoting from the conclusions of a study of different vaccines (including Salvexin+B®) published in the December 2005 issue of the NZ Veterinary Journal "**vaccines derived from** *S. brandenburg* **did not significantly protect sheep against severe experimental infection with** *S. brandenburg...*""

The Solution/Product

The intention would be to manufacture a new inactivated Salmonella vaccine for the New Zealand sheep industry containing four species; *S. hindmarsh, S. typhimurium, S. bovis-morbificans and S. brandenburg* using superior manufacturing methods including IRP Technology and Emulsigen® and seed stock. These four isolates could then be added to the current Campyvax4® formulation to form a combination vaccine. Particular interest and attention will need to be made to ensure that the efficacy of Camyvax4® is not compromised. The enteric *Salmonella* claim would have to match or better the efficacy of Salvexin+B® It is obvious that vets and farmers have become disillusioned with the ability of Salvexin®+B to control or prevent abortions caused by *S. brandenburg.* As it may be difficult to perform controlled challenge trials with S. brandenburg the protection from abortion would also be tested in the field. The initial testing to support the abortion claim would be done via a bio equivalence study. The duration of immunity would also be tested to see if it is possible to get 12 months protection from the vaccine

It is important that we maximise the protection against abortion, especially considering Salvexin®+B appear to only offer a short duration of immunity. Hence a second vaccine, a stand alone *Salmonella* vaccine that would be primarily a dedicated "S. *brandenburg* booster vaccine" would be given to ewes at scanning to ensure good protection and get over any issues that with short durations of immunity for *S.brandenburg.*

IRP Technology - for greater protection against natural challenge

Salmonellae grown in laboratory conditions are different from those found naturally in the sheep intestine. This is because nutrients such as iron are less available to natural, wild bacteria. To obtain iron, they express Iron Regulated Proteins (IRPs) on their surface, which are then recognised by the Sheep's immune system as antigens. If the vaccine is made with standard laboratory-grown bacteria (provided with high levels of iron), they never develop these IRPs, and the vaccine is deficient. However, if the salmonella vaccine is manufactured with a shortage of iron, similar to conditions in the wild, it allows the vaccinated sheep to produce extra antibodies against these IRPs. The IRP antibodies then provide greater protection against natural challenge.

Emusigen®

EMULSIGEN® is a unique oil-in-water emulsion, free of animal origin components, designed to be mixed directly with vaccine antigens, without any further processing, to enhance the immunogenicity of the finished vaccine. The manufacturing process is optimized to result in uniformly dispersed, micron-sized oil droplets which ensure maximum emulsion stability with minimal injection site tissue irritation and reactivity. Being an oil-in-water emulsion, EMULSIGEN® provides a reduction in the size of the oil droplets as well as a reduction in the quantity of oil in the final product, resulting in decreased viscosity and injection site reactions. It can eliminate or reduce the undesirable side effects associated with water-in-oil adjuvants while still eliciting the rapid and strong immune response associated with oil based adjuvants. See Appendix: 2

How does the solution meet this need?

Feature	Benefit
• Sheep farmers have been asking for this for sometime • Less vaccine jabs required • Better Efficacy • Cost effective • Use of superior manufacturing technology e.g. IRP Technology • Safer due to less endotoxin through the addition of Polymyxin B • Use of Emulsigen® • Marketable Nationwide • From Intervets point of view – a unique position of being able to over a suite of Sheep Reproduction products	• The convenience of having two vaccines in one. • Similar if not better protection from the enteric form of the disease • Improved efficacy of S. *brandenburg* component of the vaccine to what is already available. • Reduced site adverse events and possibility of deaths from vaccinating. • More profitable than current situation (Using Salvexin®+B or not vaccinating) • A form of insurance that has the potential to reduce the losses that are incurred as a result of an outbreak.

Who will buy the product?

The vaccines would be registered as a PAR 1 and therefore would be purchased by veterinarians and sold onto farmers.

This vaccine would be of particular interest to the farmers in Canterbury, Otago and Southland who are currently continuing to get hit by *S. brandenburg*. For those who vaccinate for enteric *Salmonella*, it would offer them an alternative to a vaccine that has not changed much in the last 30 years; however the main benefit would be the convenience of a combination product.

For all farmers that vaccinate against both *Salmonella* and *Campylobacter* separately at present - it would offer a combination vaccine.

Specific markets:

There are several species of *Salmonella* that cause disease in several different hosts with in the New Zealand farming industry. The opportunities for the development of a combination Salmonella/Campylobacter vaccine for the New Zealand sheep market can be divided into two specific markets:

- Farmers requiring protection against *Campylobacter* abortions, *enteric* Salmonellosis & S. *brandenburg* Canterbury, Otago and Southland
- Those seeking protection against *Campylobacte*r abortions and enteric Salmonellosis caused by *S.hindmarsh* and *S. typhimurium* in other parts of the country (mainly NI)

This market review is focused on the possible development of a new Campylobacter / Salmonella combination vaccine. It would offer the protection against *Campylobacter fetus fetus* and C. *jejuni* which is currently provided by Campyvax4® together with *Salmonella* protection, including *S. brandenburg*.

The ideal vaccine would need to achieve the same if not better results than Salvexin® +B, especially in relation to S. *brandenburg* due to the current lack of confidence held by farmers and vets.

Other potential markets identified but not analysed:

- Prevention of Salmonellosis in Cattle (Both enteric and abortion)
- Prevention of scours due to Salmonellosis for calves.
- These two other market segments would only be possible if a combination product was not achieved and the stand alone Salmonella vaccine was still developed on its own.

SWOT ANALYSIS

Strengths:

- A combination vaccine will give Intervet a market advantage with a Combo vaccine
- IRP Technology used in manufacture of salmonella vaccines should increase the vaccines response and efficacy.
- A manufacturing plant in Bendigo whose staff are experienced in manufacturing Salmonella vaccines
- Second in a market for *S. brandenburg* when there is not a lot of confidence in Salvexin®+B.
- Intervets knowledge and experience in the NZ sheep vaccine business
- Serology technology

Weaknesses

- Risk of not getting superior *S. brandenburg* efficacy and the same if not better efficacy for enteric salmonellosis.
- Risk of a combination vaccine not being possible
- Risk of challenge and field trials failing
- Strain selection for manufacture for *S.hindmarsh*
- Adjuvant choice – Farmer reaction?

Opportunities

- Delivering a combination vaccine that farmers have been asking of the industry for years.
- Creation of a vaccine with superior claims for enteric and abortive salmonellosis.
- Adjuvant Choice – should enable much higher vaccine titres.
- Possible lack of gram negative effects due to limiting endotoxin at point of manufacture together with the addition of polymyxin B.
- Grow the current market – All those vaccinating for either Campylobacter of Salmonella will no have the option of a combination.
- Create a vaccine with better duration of immunity offering 12 months protection for all species in the vaccine.
- Reduce the number of systemic reactions.
- Leverage of our existing abortion vaccines, making us clearly the market leader in the area.

Threats

- Eights antigens in one combo vaccine does not produce the desired result.
- The Salmonella components of the new vaccine is not as effective as we would hope therefore giving no advantage over Salvexin+B®
- Poor duration of immunity for *enteric Salmonella* and *S. Brandenburg*
- In light of a resurgence of S.*brandenberg* throughout Southland and Otago in 2005, Schering Plough beat us to the market with an improved vaccine.
- Farmer & vet scepticism
- SPAH discounting of Salvexin®+B to maintain market share if the new vaccine is shown to be making an impact in the market.
- The changing pattern and challenge of disease – both enteric and abortion causing salmonellosis.
- Second to market – therefore we will face a lot of initial challenge from our competitor
- Farmers are sceptical of S. *brandenburg* vaccine at present – market is damaged.
- Vet loyalty to Schering Plough Animal Health & their historic rebate structure.

Intervet NZ has a wealth of experience in the area of NZ sheep veterinary medicine, specialising in the area of reproduction. Our colleagues at Intervet Australia in Bendigo have a wealth of knowledge and experience in the development of *Salmonella* vaccines. Our Campyvax 4® is also manufactured at Bendigo, therefore making a vaccine blend reasonably straight forward in terms of manufacture. A combination vaccine for sheep would fit the Intervet sheep biologicals suite of vaccines very well. There would still be a need to have Campyvax4® available as a stand alone vaccine as there are a number of sheep regions in New Zealand that are fortunate enough not to have a salmonella problem.

It is hoped that a competitive advantage would be gained through a greater level of protection and a longer duration of immunity gained from the likes of adjuvant choice and IRP technology utilised in manufacture. Ideally the benefits of this would be seen across all four serotypes in the vaccine giving the salmonella component a distinct advantage over its competitor. If we could achieve 12 month duration of immunity claim then we would negate the need to have a "booster vaccine" for protection against S.*brandenburg.*

A combination product is a huge competitive advantage on its own, let alone any efficacy or duration of immunity benefits.

Market Statistics

The Macro Market

The macro market would be all replacement ewe hoggets or two tooths being mated for the first time. There would be a requirement for these animals to receive two initial doses of the combination vaccine in the first year. It would be likely that as a result of data collected that a booster dose be given in early summer in the following years.

In terms of the S.*brandenburg* booster vaccine requirements – this would be administered annually to all ewes in the flock at approx day 90 of gestation which would coincide with scanning. As stated earlier if we had 12 months duration of immunity claim then this would negate the need for a stand alone Salmonella booster vaccine.

An estimate of replacement numbers has been determined by adding the number of ewe hoggets put to the ram in 2005, plus ewe hoggets not put to the ram in 2004 (hoggets that have been carried over and mated for the first time as two tooths) This calculation assumes that all ewes that live to be hoggets, will at some stage, either as a hogget or a two tooth, enter the breeding flock.

The total number of replacement stock entering the flock in NZ each year is calculated to be approximately 7,961,674. This works out to a national replacement percentage of 27% (replacements as a percentage of total NZ breeding ewes). The replacement rate in the North Island was slightly higher (29.8%) compared to the South Island (24.6%).

Calculating the potential market is required to be carried out for firstly the combination vaccine and then for the S. *brandenburg* stand alone booster vaccine.

Combination Vaccine

Geographically this vaccine would be used in regions that are currently vaccinating for enteric *Salmonella* as well as those vaccinating for S.*brandenburg*. This would include: Gisborne, Wanganui, Rangetiki/Manawatu, Hawkes Bay, Wairarapa, South & Mid Canterbury, Otago and Southland.

Salmonella Booster Vaccine

The booster vaccine for *S. brandenburg* would be specific to South & Mid Canterbury, Otago and Southland. Although there have been unconfirmed reports of a recent outbreak in North Canterbury by a veterinarian in Cheviot.

Total Sheep Numbers By Region

Total ewes put to the ram for the 2005/06 year can be seen in the table below. From these figures approximate figures can be obtained to estimate the size of the market for both vaccines.

Region	Replacements	Ewes To Ram
Gisborne	318,631	1,274,525
Manawatu	1,265,449	5,061,796
Hawkes Bay	692,983	2,771,930
Wellington /Wairarapa	381,768	1,527,070
Canterbury	1,316,048	5,264,912
Otago	1,149,032	4,596,128
Southland	1,237,283	4,949,130
Total	**6,361,194**	**25,445,491**

Maximum Combination Vaccine Market Potential – "CamSal"

This vaccine requires two doses initially as a hogget or a two tooth (first mating). Then a booster dose would be required annually thereafter. However it is a fact of life that at present there is a large number of farmers that will give the two initial doses and then leave any annual booster vaccinations unless there is a perceived additional risk.

Region	Year 1(V 1&2)	Enteric Booster
Gisborne	637,262	955,894
Manawatu	2,530,898	3,796,347
Hawkes Bay	1,385,966	2,078,947
Wellington /Wairarapa	763,536	1,145,302
Canterbury	2,632,096	3,948,864
Otago	2,298,064	3,447,096
Southland	2,474,566	3,711,847
Total	**12,722,388**	**19,084,297**

At present the market is made up of three segments; the first two segment are made up of those farmers currently vaccinating for Campylobacter using either Campyvax4® or Campylovexin®, the third segment is made up of those farmers vaccinating with Salvexin®+B or both. These three segments are currently at equal proportions.

It is estimated that over the first six years of the new combination and our stand alone Salmonella vaccine being on the market the combination (CamSal) would take 30% of the current market in the first year of launch extending out to 57% of the market six years after launching. **See Appendix: 3**

N.B. Of the maximum total market it is estimated that approximately 65% – 70% of replacements are vaccinated either with a Campylobacter or Salmonella vaccine. The number receiving annual boosters is estimated to be closer to 45%

Booster Vaccine Market Potential – "Salvax"

The booster vaccine for S.*brandenburg* would be predominantly South & Mid Canterbury, Otago and Southland. As stated this will be a stand alone Salmonella vaccine used for the purpose of boosting the immunity to *S.brandenburg.*

The approx. number of replacement are as follows:

Canterbury	1,316,048
Otago	1,149,032
Southland	1,237,283
Total	3,702,363

The Stand alone Salmonella vaccine used for boosting *S.brandenburg* would start in the first year of launch at 7.7% of the total market extending out to 12.3% of the total market six years after launching. It must be remembered that we will be eroding into our current Campyvax4® sales. **See Appendix: 3**

Target Market

The target market for this new vaccine is in the regions as described above by offering farmers an alternative to having two individual vaccines, instead offering them a combination vaccine. For those in Southland Otago and parts of Canterbury we would be targeting all farmers wishing to protect their flocks against *Campylobacter*, enteric *Salmonella* and S.*brandenburg.*

	Year 1	**Year 2**	**Year 3**
Enteric	V1 & V2 Combination	V3 Combination	V4 Combination
Brandenburg Abortion	V1 & V2 Combination + S.b Booster	V3 +S.b Boost	V4 +S.b Boost

***** *S.b Boost is the stand alone salmonella vaccine administered at scanning (approx. day 90 of gestation)*

If we can achieve 12 months duration of immunity for the combination vaccine including S.brandenburg then we would not need the stand alone salmonella vaccine.

Value Chain

Market Research → R&D → Manufacture → Sales → Support

Currently we are in the Market Research and R&D stage – our intention is to operate in the manufacture sales and support area.

End Market – Who will buy this Product?

These two vaccines will be sold to farmers via a prescription from their local veterinarian. The vaccines will be registered as a PAR 1.

Market Description – embryonic, growing, or mature?

The initial market is in NZ particularly for S. *brandenburg* as this form of the disease is NZ specific. However there may be scope in the future for the combination vaccine to be marketed in Australia and other parts of the world where Salmonella and Campylobacter cause problems in sheep. However this has not been researched or modelled.

The end-users (farmers) in this market have been using Salvexin® +B for many years. For the S. *brandenburg* this has been with limited success, however as stated earlier this vaccine has been excellent in controlling the enteric form of this disease. Farmers have also been using a *Campylobacter* vaccine for over 20 years. In 2005 Intervet launched Campyvax4® which has the added value of C.jejuni. These same farmers have been continually asking the question about multi antigen combination vaccines for a number of years. This new vaccine will give them this – therefore our goal is to provide these farmers with a better solution for those farmers that have been vaccinating for *Campylobacter* and *Salmonella* separately by offering them a combination vaccine as well as grow the market. The difficulty will be dealing with the possibility of a damaged market due to the inefficiencies of Salvexin® +B to give the desired protection against *S. brandenburg.*

Competitors

Schering Plough Animal Health has an inactivated *Salmonella* vaccine called Salvexin® + B. This is the only *Salmonella* vaccine with a sheep registration claim currently on the NZ market. The original product was simply known as Salvexin® (containing S. *hindmarsh*, S. *typhimurium* and S. *bovis-morbivicans)*. This has been available for over 20 years. In 1999 *S. brandenburg* was added to the vaccine hence the name changed to Salvexin® +B. This has increased the penetration in the lower South Island. Therefore Salvexin®+B enjoys100% of the market.

Schering Plough Animal Health also have Campylovexin® vaccine which is the competitor Campylobacter vaccine to Campyvax4® however it lacks C.*jejuni* and only contains a single serotype of C. *fetus fetus*. (See the Intervet Camyvax4® technical manual if more detail is required) Campyvax4® and Campylovexin® would currently each share 50% of the market.

The introduction of a combination Campylobacter / Salmonella vaccine would be a market first for NZ and would be well received as evidence by market feed back.

What makes this competitor successful?

SPAH has the only *Salmonella* vaccine available for the use in sheep in NZ. They have excellent relationships with the market (veterinarians) which is an important factor as well as the multiple claims for different *salmonella* species and different hosts. Cattle would be a good example as a different host as it is well known that enteric *S. brandenburg*. We would be making no initial claim for cattle but it is possible that vets may use the vaccine off label.

Who are potential competitors to this market?

At this point in time there are no other vaccines on the market for *salmonella* and *campylobacter* as a combination. However as a result of Intervet introducing a combination vaccine SPAH could well react with one of their own, however this would erode the very high margins they enjoy with the separate vaccines

What are the barriers to entry to this market?

The biggest barrier to entry into this market is the likelihood of technical success of the trial work that is necessary to get the new vaccine to market.

In NZ *Salmonella* and in particular *S brandenburg* natural infections are sporadic making it difficult to create effective challenge models necessary for effective R&D trials. Challenge models for the enteric form of the disease are available in the literature and from our colleagues in Australia.
The effects of a gram –ve vaccine are well known and with this particular vaccine we are attempting to combine two gram –ve vaccines which could possibly cause

problems due to endotoxin effects. This can lead to sheep being dull and a loss of appetite for a few days following vaccination. In a worse case scenario the effects of endotoxins can cause the sheep to die. It is hoped that by using Polymyxin B in our vaccine we can reduce the chance of these effects, seen in other gram –ve vaccines.

The entrance of another player into this market in the future can not be totally ruled out, but would be seen as unlikely given the size of the market.

Are other similar products or solutions under development?

As far as we are aware there are no similar products or solutions under development, however we do know that SPAH are likely to be looking at a possible way of regaining their market share for Campylovexin®.

There is a live Salmonella vaccine available in New Zealand which is only registered for the poultry industry. This vaccine is known as Meganvac1 and is registered and distributed by Pacificvet. There have been some trials carried out in sheep specifically to address *S. brandenburg* in sheep. In 2001 a group from Lincoln University presented a safety study in pregnant ewes to the NZ Society of Animal Production Conference in which a subcutaneous injection of 10^{10} vaccine organisms actually caused abortions. However, the paper went on to say that the efficacy trials were underway using lower doses. (Li Hong, RG McFarlane, J Wagner, 2001)

In 2001, the same group were also involved in a Risk Assessment Group with MAF about *S.brandenburg* abortions. They presented a paper showing some (insignificant) efficacy of the vaccine in preventing experimental abortions due to *S.brandenburg* when delivered by intra-ocular drop. This was confirmed by a poster written by Li Hong, a PhD student at Lincoln University in 2003.

Informal reports from veterinarians involved in field trials of this vaccine concluded that the vaccine had no noticeable effect and subsequently the project has been discontinued.

Intellectual Property (IP)

What is the exact current situation with IP in this proposal?

The IP required for this project already exists in part due to the fact that Intervet own all but one of the antigens involved. The only strain that we will need to obtain is S. *hindmarsh* to ensure we have the same strains of *Salmonella* in the combination and stand alone salmonella booster vaccine that can be found in Salvexin® +B.

The combination vaccine if successful will be novel and therefore should be patentable.

Infringe third party patents.

No

Securing of any Intellectual Property.

A contract with AgResearch Infectious Diseases Group

Science/Technology/Product development

What scientific evidence is there that the concept can succeed?

This vaccine has been requested by many farmers and vets over a number of years. However this type of technology is not simple and requires a lot of thought from conception of the idea to the potential launch of a new vaccine. As a combination vaccine it offers NZ farmers a solution to combating two diseases that are detrimental to production on the farm.

We need to ensure that the efficacy of the Campyvax4® components of the vaccine is not compromised. The endotoxin issues caused by gram –ve vaccines needs to be established. This will include looking at the effect of the possibility of adding Polymyxin B to the vaccine to try to reduce the effect.

Polymyxin B (also referred to as PMB) are antibiotics primarily used for resistant gram negative infections. Polymyxins bind to the cell membrane and alters its structure making it more permeable. The resulting water uptake leads to cell death. They are cationic, basic proteins that act like detergents. Polymyxin B has been used in NZ in a topical antibiotic registered by the ACVM and is approved by ERMA.

The choice of adjuvant will also be important to help achieve the desired result. At this point we are looking at plant based oil in water adjuvant (Emulsigen®) which has been shown to have good results with *Salmonella* vaccines overseas. There is a need to check if this adjuvant will stimulate the same responses to the Campylobacter antigens as DEAE dextran does in Campyvax4®.

An efficacy challenge trial would need to be completed for a robust enteric claim for the vaccine. This would be carried out in a PS2 facility. Safety trials will need to be carried out in. These would follow an existing protocol.

The sporadic nature of natural infection and inconsistent immulogical parameters of protection for *S. brandenburg* means that it is best to demonstrate artificial efficacy in an infection model. However creating an experimental model of infection has been very difficult. **Both SPAH and Pacific Vet have reported their inability to create a meaningful model**. However, both companies have used their products in the field – SPAH has shown some efficacy based on the power of large numbers of animals over a number of years after the addition of the *S. brandenburg* strain to Salvexin®. Pacific Vet conducted field trials that proved to be inconclusive.

We would use the same strategy as SPAH and repeat i/v challenges at various infection doses SPAH state in their pack insert "The level of protection provided by Salvexin®+B against Salmonella *brandenburg* has not yet been fully established. Consult your veterinarian." We would be seeking no specific claim initially for the S.*brandenberg*. Intervets intention would be to target the market by hopefully having a vaccine with a better adjuvant, lower gram –ve effects, and most importantly the potential of a combination vaccine.

A decision tree can be seen in Appendix: 4

Are we utilising new or proven technology? Describe, including risks.

We have established that Campyvax4® is an effective vaccine in protecting against C. *fetus fetus* and aids in the control of C.*jejuni*. There is a need to implement 4 salmonella antigens in the vaccine to enable Intervet to have the same antigens to that of Salvexin®+B.

This project has a number of risks and option available to us as we move through the R&D process and we will need to carry out costings on the following options so that we know what our next option is if one part fails.

	Brandenburg Boost Required	Enteric Claim	Abortion Claim
1. Combo Vaccine with 12 mths DOI	No	≥ Salvexin®+B	>> Salvexin®+B
2. Combo Vaccine	Yes	≥ Salvexin®+B	>> Salvexin®+B
3. Combo Benefit Only	Yes	= Salvexin®+B	= Salvexin®+B
4. Enteric Combo Only	N/A	= Salvexin®+B	= Salvexin®+B
5. Salmonella Vaccine Only	N/A	≥ Salvexin®+B	>> Salvexin®+B
6. Salmonella Vaccine Only	N/A	= Salvexin®+B	= Salvexin®+B

What are the different phases in the development cycle, and what is the cost and probability of success around each phase?

- ***Scientific/Technical Requirements***:

See Appendix: 5

- ***Regulatory Requirements***:

Successful challenge trial for a scours claim and sufficient safety data to satisfy the ACVM.
The use of the use of Polymyxin B in NZ may need to be clarified with ERMA; however it is used in other animal and human pharmaceutical products.
We would also have to make a presentation to the Animal Ethics Committee to get their approval for the challenge trials.

- ***Intellectual Property Management*:**

The majority of the IP is currently owned by Intervet Ltd with the exception of a S. *hindmarsh* antigen which will be found from outside the company. There is the possibility of obtaining further IP during the development and production of this vaccine.
The IP in IRP technology is already within Intervet.

Production/Operations

Vaccine Production / Manufacture.

These vaccines would be manufactured at Intervet Australia Ltd in Bendigo and then sent to Intervet NZ Ltd in Upper Hutt. It would be presented in a ready to use (RTU) formulation in a 100ml and 500ml vaxipack. The ideal and desired dose rate would be 1ml; however it is more than likely that it would need to be a 2ml dose. The registered shelf life for this vaccine would ideally be out to 18 months.

From a production/operations perspective, what are the actions required in order to develop the product?

We need to develop and test technologies and trial formulations.
As stated we will need approval for the S.*hindmarsh* antigen and investigate the use of Polymyxin B to help deal with possible issues with high endotoxins through trying to formulate a vaccine containing a total of eight gram –ve bacterial strains.
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Sales and Distribution

Who would sell this vaccine?

The product will be sold as a PAR class 1 and only be available to farmers following gaining a prescription from a veterinarian.

From a sales and distribution perspective, what are the actions required in order to develop the product?

This product will fit into the continuing market position that Intervet have in NZ, as a result of the purchase of Agvax – that being "Sheep Reproduction Specialist" The vaccine will complement our other three current Sheep Reproduction vaccines; Toxovax®, Campyvax4® and Androvax®.

The launch would be similar to that of Campyvax4® in which a series of events to veterinarians, scheduled in the key regions which will focus on the meaningful technical information and the fact that it would be a combination vaccine that has been demanded for a number of years. Veterinary and rural media would be targeted using editorial work and advertising to get our story out to the NZ sheep farmer.

As has been the case with the other vaccines mentioned we would also intend to run presentation alongside our veterinary clients and to maintain a presence at monitor farm days as part of the Farm Monitor programme run through Meat & Wool NZ.

Our sales approach would be to provide a significant level of technical support used in the launch of the vaccine and continue to develop our position of having expertise in sheep reproduction. This will become increasingly important in terms of the Southland, Otago, Canterbury regions where the *S. brandenburg* component of the vaccine will initially be challenged by both vets and farmers. The key to this will be demonstrating that the new vaccines have trial work that is good and proves that it offers protection. If this can be done then vet and farmer acceptance should be good too.

People

List the internal resources required, describe the competencies they bring, and the expected work effort.

Alex Walker, Nick Gorman (Project Managers)
Robert Dempster (R& D technical adviser)
Paul Ralph (Marketing & Analysis)
Neil Sammons (Head of Manufacturing – Intervet Australia)
Geoff de Lisle (Agresearch, Wallaceville)
Invoco Ltd (Trial work)

Give specific evidence of team or individual track records in previously commercialising products or concepts?

All the above have been involved in Intervet's most recent commercial vaccine launch – Campyvax4® which was in 2005.

Robert Dempster and Alex Walker have a wealth of knowledge and experience with bacterial vaccination, and are aware of the requirements for registration purposes.

Geoff de Lisle was the R&D manager for the development of Campyvax3® the predecessor for Campyvax4®. He has experience with bacterial vaccination and Salmonella expertise. He is also aware standards required for registration purposes.

Neil Sammons is the Head of Manufacturing at Intervet Australia – he also has a wealth of knowledge and experience with bacterial vaccination and manufacturing and production processes.

Project Milestones, Timelines

Milestone	Time
Availability of *S.hindmarsh*	1
Blending of Vaccine	1
Provisional Registration	2
Investigating Endotoxin issues	3
Scours Efficacy trials + effect of Cx4 antigens	3
Duration of Immunity Inc. *S.brandenburg* Challenge and field trials	12
Registration	3
Marketing	2
Launch	
Time To Market	2.5 years

Group Strategy/Marketing

How does this proposal support the strategic plan of Intervet NZ Ltd?

It enables Intervet to launch a new vaccine 3 years after launching Campyvax4® that would add considerable stature and value to complement our other three Sheep Reproduction vaccines.

The NZ Sheep farmer has been asking for a combination vaccine such as this for quite some time at various meeting and via the rural press. This would give Intervet a profile at point of launch as having listened to the customer when Campyvax4® was launched and as a result a combination vaccine including Salmonella had researched and brought to market in a relatively short time period.

This would position Intervet as the number one supplier of sheep abortion vaccines in New Zealand.

Which of our core capabilities does this proposal exploit?

Intervet has experience in developing, marketing, and distributing bacterial vaccines as well as a wide range of other animal pharmaceuticals. In the area of Sheep reproduction we have the ability to deliver a high level of technical support at both a vet and farmer level.

Reliance on external parties?

For the supply of a S. *hindmarsh* strain – AgResearch (AgR)
We would also look to AgR to help us with the Scours efficacy trail and utilise their PS2 lab.

Are there overlaps to other subsidiary companies or projects?

The adoption of this combination vaccine in the areas affected would mean that it would be in place of a stand alone Campylobacter or Salmonella vaccine. Where a farmer was using Cx4 – this new vaccine would be used in its place.

Conclusion

In completing this report a number of issues have come to light and it is obvious that the idea of a combination vaccine is not as simple as blending different antigens together with an adjuvant to form a new vaccine.

It is believed however that this particular vaccine is indeed possible; however there are a number of hurdles to cross throughout the research and development phase. There are also a number of other options available if one part of the development phase fails.

The ultimate goal is to have a combination *Salmonella Campylobacter* vaccine on the market and this has been echoed through voice of customer in terms of the advantages of a combination vaccine and the need for a vaccine that offers better protection against *S. brandenburg.*

References:

1. **Bruere A.N, West D.M 1993. The Sheep – Health, Disease & Production pg 274-279. Veterinary Continuing Education, Massey University**
2. **Bruere A.N,Ridler A & West D.M. 2002. The Sheep – Health, Disease & Production**
3. **Hicks J. 2006. Otautau Vets Newsletter January 2006**
4. **Hong L, McFarlane R.G, Wagner J. 2005. Vaccination of pregnant ewes against infection with Salmonella Brandenburg. NZ Vet Journal 53(6) 416 – 422.**
5. **Hong L, McFarlane R.G. 2001. Scientific Paper. Protective immunity to Salmonella Brandenburg infection.**
6. **Intervet Website…… http://www.intervet.com**
7. **Schering Plough Animal Health Website…..Salvexin®+B http://www.spah.co.nz/product_detail.html?pi=69**

Appendix: 1

Salmonella Farmer & Vet Survey July 2006

Area Surveyed: NZ Wide – Majority of the respondents were from Southland & Otago.

Number Surveyed: 40 vets & 50 farmers

Responses: 22 vets & 24 farmers

Summary of Results:

1. Importance of Salmonella to farm productivity:
   - Enteric - Moderate
   - Abortion - High

2. Percentage of vaccine purchases relating to:

   - Enteric - 40%
   - Abortion - 60%

3. Current vaccine rating:

   - Protection from enteric Salmonella - High
   - Protection from *S. brandenburg* - Low – Mod.

4. Uptake of a combination vaccine:

   - With abortion claims no better than Salvexin®+B - 15%
   - With superior abortion claims - 100%
   - With enteric claims no better than Salvexin®+B - 100%
   - Superior enteric claims - 100%

5. Pricing

   - Range: 0.26c – $1.50 per dose
   - 75% of respondents said they would be prepared to pay between 0.90c & $1.10 for the benefits of a combination vaccine.
   - The respondents that said they would pay more than $1.10 would so if the abortion claim was superior to that of Salvexin®+B.

6. Current vaccination strategy

- Don't vaccinate - 58%
- Early Summer - 12%
- Pre mating - 7%
- Post mating - 5%
- On Demand - 18%

Of those that did not vaccinate almost 87% of them were from Southland/Otago and had vaccinated in the past but had stopped due to not getting the desired result.

7. The ideal vaccine?

- Better protection
- Better duration of immunity
- Cost effective
- Time saving

Appendix 2

EMULSIGEN®

(oil-in-water emulsified adjuvant)

Technical Bulletin

Summary of key points:

- ☐ Stable mineral oil-in-water emulsion
- ☐ Consistent particle size, 1 — 2 microns
- ☐ Sterile
- ☐ Ready to add to antigen, no further processing required
- ☐ Neutral pH
- ☐ In use since 1983—demonstrated safety
- ☐ Components on Annex II and/or various GRAS lists
- ☐ No Animal Origin Components

EMULSIGEN® is a unique oil-in-water emulsion, free of animal origin components, designed to be mixed directly with vaccine antigens, without any further processing, to enhance the immunogenicity of the finished vaccine. The manufacturing process is optimized to result in uniformly dispersed, micron-sized oil droplets which ensure maximum emulsion stability with minimal injection site tissue irritation and reactivity.

Being an oil-in-water emulsion, EMULSIGEN® provides a reduction in the size of the oil droplets as well as a reduction in the quantity of oil in the final product, resulting in decreased viscosity and injection site reactions. It can eliminate or reduce the undesirable side effects associated with water-in-oil adjuvants while still eliciting the rapid and strong immune response associated with oil based adjuvants.

Oil-in-water emulsion adjuvants act by forming a mobile depot of antigen which can target immune effector cells. The depot effect with slow release improves the presentation of antigen and provides a significant enhancement of the immune response and effectiveness of the vaccine.

EMULSIGEN® can be used alone or in combination with aluminum hydroxide, CARBIGEN™, and other adjuvants or immune stimulators, depending on your needs and applications, and may be administered parenterally in a wide variety of species of large and small animals.

Information about EMULSIGEN®

Immune Response: EMULSIGEN® has the potential to elicit higher levels of humoral antibody, more rapid onset of immunity, and enhanced protection with a single vaccine dose as compared with conventional aluminum based adjuvants. It may be used in inactivated bacterial, Mycoplasma, viral or subunit vaccines.

Animal Safety: Because it is prepared from pharmaceutical grade oil and is comprised of uniformly dispersed micron-sized oil droplets, EMULSIGEN® is less likely to result in tissue reactions occasionally seen with products containing conventional oil adjuvants.

Consumer Safety: The lipid component of EMULSIGEN® is a pharmaceutical grade light mineral oil. Other ingredients, including emulsifying agents, are NF grade, on Annex II, and/or have been approved by FDA for use in foods and by the USDA for use in veterinary vaccines.

Esthetics: EMULSIGEN® is a milky-white emulsion and creates a smooth, uniform mixture to enhance vaccine appearance when added to your veterinary antigen component.

Convenience: EMULSIGEN® is easy to use. It is sterile and mixes easily with water-based antigens. Sophisticated laboratory equipment is not required, and further processing is neither necessary nor recommended prior to use.

Stability: MVP utilizes HLB (Hydrophile-Lipophile Balance) technology to maximize stability of the oil-in-water emulsion. Use of HLB technology results in oil droplets of uniform micron size, thereby eliminating problems related to undesirable product separation and poor syringeability.

Syringeability: Vaccines containing up to 50% EMULSIGEN® easily pass through a 25 gauge needle at 10°C (50°F).

Uniformity: The use of highly skilled operators, modern equipment and standardized manufacturing procedures ensures that each batch of EMULSIGEN® will be consistent, uniform, and comply with specifications.

Preservatives: EMULSIGEN® is normally available with formaldehyde (< 740 ppm) and/or gentamicin (30 mcg/ml) as preservatives. Other preservative combinations are available upon request. It is also available without preservatives if desired.

Ingredients: Each lot of EMULSIGEN® is manufactured to the highest standards using the finest components available. All ingredients are refined, processed or synthesized in the United States and meet United States Pharmacopoeia (USP), National Formulary (NF) or equivalent specifications. **EMULSIGEN® contains no animal origin ingredients**. All components, including the containers, are sterilized prior to use to ensure sterility of the final product.

Testing: Each ingredient contained in EMULSIGEN® must meet stringent in-house parameters for purity and consistency. Each lot is thoroughly tested to ensure that it is free of viable bacteria and fungi. Viscosity, pH and formaldehyde content of the finished adjuvant (if applicable), as well as its macroscopic and microscopic appearance and particle size, are carefully monitored to maintain batch-to-batch uniformity and stability.

Storage: EMULSIGEN® may be stored at 4° - 25°C (39° - 77°F). Temperature extremes should be avoided.

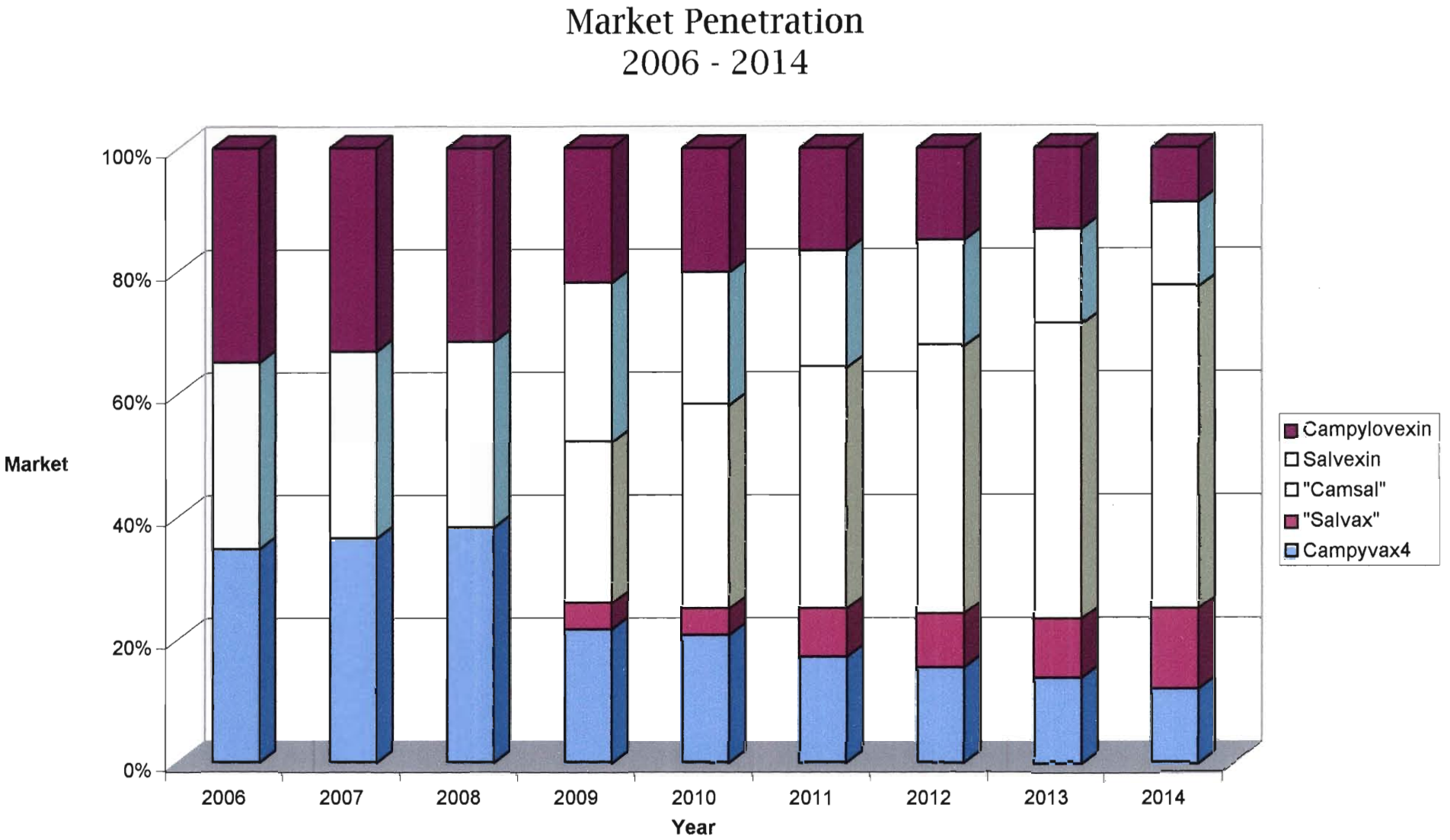
Packaging: EMULSIGEN® is available in 10 and 20 liter container sizes. Other sizes can be provided to meet each customer's needs. EMULSIGEN® can also be provided in sterile bags.

Instructions for Use

1) For most bacterial and viral antigens, we recommend that EMULSIGEN® be added at a ratio of 1 part EMULSIGEN® to 4 parts antigen (20%) and mixed thoroughly.
2) For soluble antigens such as Gram positive toxoids and Gram negative endotoxins, we recommend the use of EMULSIGEN® in combination with an aluminum hydroxide adjuvant such as Rehydragel®-LV. In this case, aluminum hydroxide adjuvant should be added first at 5% of the final volume, mixed about one hour, then EMULSIGEN® should be added at 15% by volume and mixed thoroughly.
3) EMULSIGEN® should be thoroughly mixed before adding to the product. The adjuvant can be added to the inactivated liquid cultures and mixed using ordinary mixing equipment. There is no heat generated by, or necessary for, mixing of the culture with this adjuvant. No special equipment is needed but aseptic technique is required.
4) After thorough mixing, the product is ready to fill. Mixing should continue throughout the filling process.
5) Products containing EMULSIGEN® may be administered intramuscularly or subcutaneously in a wide variety of both large and small animals.

MVP Laboratories, Inc.
4805 "G" Street, Omaha, Nebraska 68117, USA
Telephone: (402) 331-5106 Telefax: (402) 331-8776
mvplabs@mvplabs.com / www.mvplabs.com

Appendix 3


Market Penetration
2006 - 2014
Market
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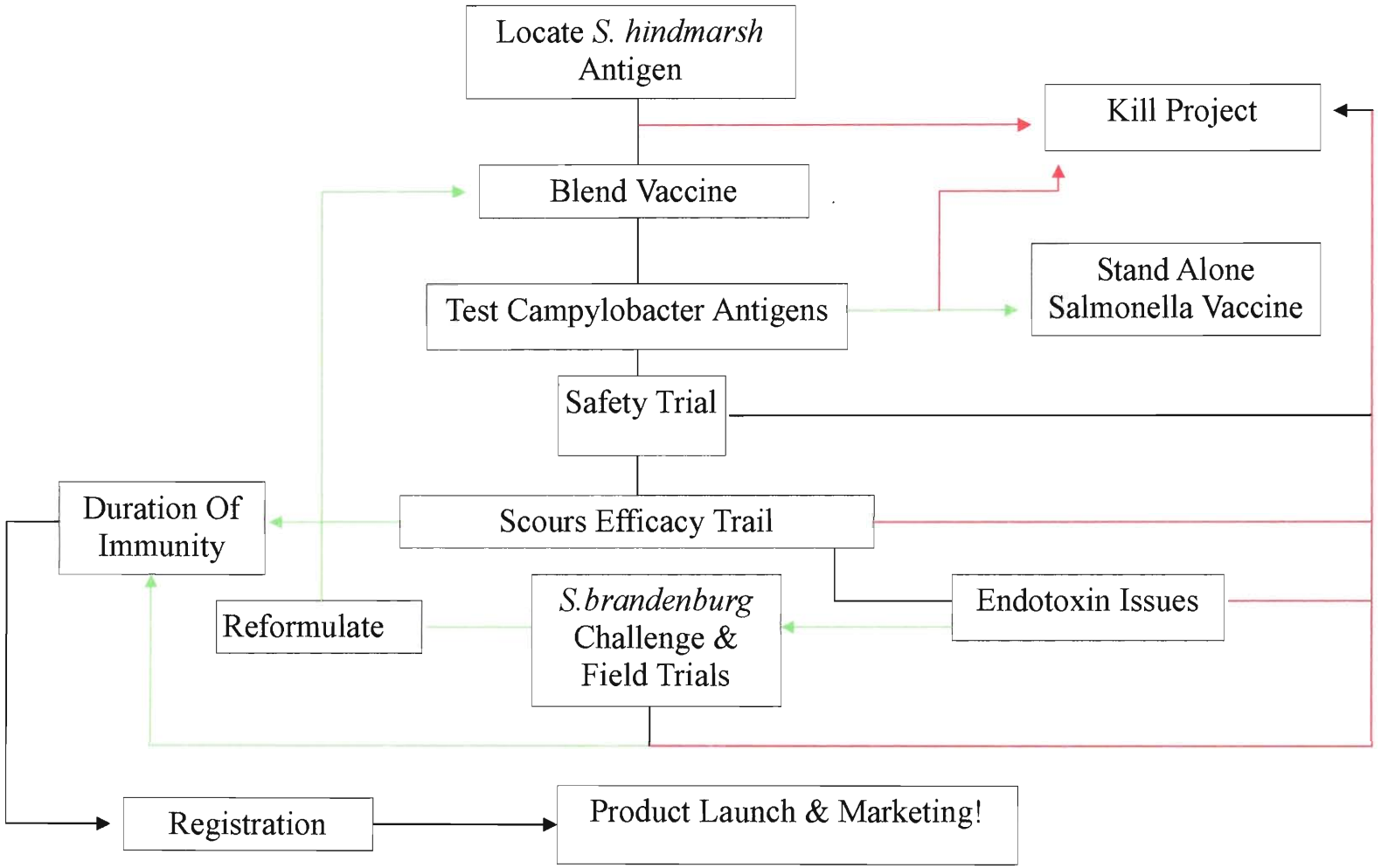
80%
60%
40%
20%
0%
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
Campylovexin
Salvexin
"Camsal"
"Salvax"
Campyvax4

Appendix 4:

Campylobacter / Salmonella Vaccine Decision Tree



Appendix 5:

Technological Risks – *Campy/Salmonella* vaccine and separate *Salmonella* vaccine

Task/Trial	Detail	Risks	Probability of success	If fail then ...
Develop test technologies	Measure specific antibody responses to each *Salmonella* species			
Safety and Campy serology trial	Assess safety of 6 formulations and test impact on *Campylobacter* serology	Campy responses poor Safety fails	Medium High	Develop separate Salmonella vaccine Reformulate, increase Polymyxin B conc.
Develop eneteric challenge model	Get AEC approval for death as an endpoint. Trial different oral challenge doses of 2 *Salmonella* species	AEC approval Model is poor or non-reproducible	Medium High	? Try other isolates, other concs
Complete enteric trial	2 vaccines, +ve and –ve controls. 2 time points, 2 challenge species = 240 sheep	Model not reproducible DOI poor at 6 months Salvexin as good or better	High Medium High-medium	Repeat Consider alternative usage pattern Concentrate on *S.brandenburg* claim
Develop *S.brandenburg* abortion challenge model	Use i/v at various doses to induce abortion	No reproducible model developed	Medium-low	Field trial

Complete *S.brandenburg* abortion trial	2 vaccine use patterns, +ve and –ve controls. 1-2 time points, 2 challenge species = 240 sheep	Model not reproducible Booster needed as well Salvexin as good or better	Medium Medium High-medium	Repeat OK Bugger !
Complete field trial	20 farms for 1-3 years while vaccine is sold	No natural challenge Salvexin as good	Medium By now High	Repeat Bugger !