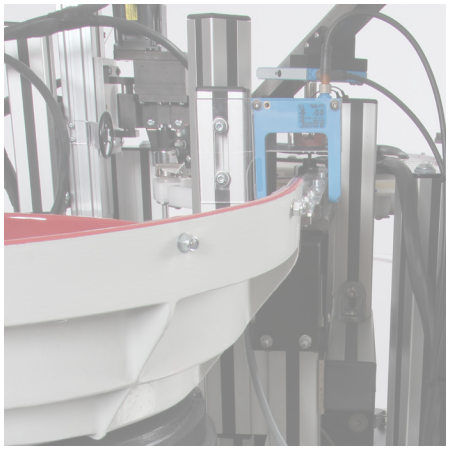


Barbervax® Commercial Vaccine Production System

Client Company: Moredun Research Institute / Wormvax Ltd

Design Consultancy: 4c Design

Submission Date: November 2018

Barbervax® Commercial Vaccine Production System in use by our client, Dr David Smith

"When we started this project we didn't know if it could be done. 4c have designed practical machines that have enabled the creation of a new international business."

Dr David Smith

Executive Summary

Barber's Pole worm is a parasitic nematode that infects the gut of sheep and goats in hot, humid climates. For farmers in such regions an infestation can be economically devastating as these blood-sucking, treatment resistant parasites spread quickly causing anaemia and ultimately death of entire flocks.

The Problem

After 20 years of research, Dr David Smith's team of veterinary scientists at Edinburgh's Moredun Research Institute had developed the first vaccine for the Barber's Pole worm. Making the vaccine involves grinding up worms taken from the stomachs of dead sheep. Although the process was successful at lab-scale, to be commercially viable a production process and equipment needed to be designed which could operate at the same rate as Australian abattoirs. No equipment capable of the task was available and a bespoke solution was required. 4c were engaged by Dr Smith to design and build a commercial production system that could harvest the worms and bottle the vaccine in a way that would be reliable, cost-effective and semi-automated.

4c Solution

Our design solution, made up of three separate production machines, was invented, developed and built in our workshop, then shipped to our client's site in Australia where we installed and commissioned the machines. When Barbervax® (the Barber's Pole worm vaccine) was launched in Australia in 2014 the 300,000 dose production run was a sell-out success. Since then, production has grown rapidly to 2.5m doses in 2017-18, all produced by the machines designed and built by 4c.

Commercial Outcomes

Our design solution enabled Dr Smith to achieve his objective of producing Barbervax® at commercial scale and making it available to farmers to protect their sheep and livelihood. Our design input was a key enabler for Dr Smith and his colleagues at the Moredun Research Institute, who have raised over $1m AUD to set up a new business, Wormvax, to produce Barbervax®. Wormvax now employ 8 people and have launched the vaccine in Australia and South Africa with other markets planned. Wormvax is operating profitably, generating return on investment and above all, protecting a rapidly increasing number of sheep from a deadly parasite – over 500,000 sheep worth between $30m and $85m AUD were protected in 2017-18.

Case Study Overview

Project Brief

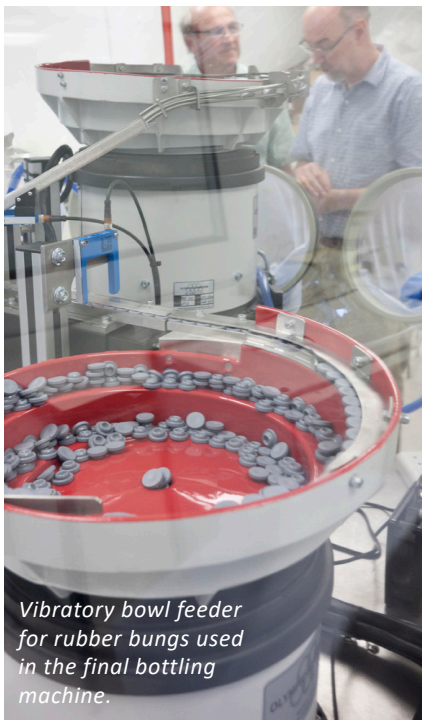
Objective: to enable commercial-scale production of the Barbervax® vaccine

4c's initial brief was to investigate the feasibility of designing a new manufacturing process and equipment which would enable Dr David Smith's laboratory work-flow for vaccine production to be scaled up. Without this process and equipment, he was unable to produce the vaccine in large enough volumes to be commercially viable. Our client, Moredun Research Institute, hoped that 4c could design and build a system which would enable them to start up a new business to produce and sell the vaccine. At the outset of the project neither we, nor Dr Smith, were certain that this was achievable.

After considering design options, developing proof of concept prototypes and proving feasibility, 4c worked with Dr Smith and his team to develop a design brief for the full production system, comprising three reliable, cost-effective and semi-automated machines. We were then contracted to design and build the full system, followed by installation and commissioning at our client's site in Australia.

In order to achieve the goal of commercially viable vaccine production our design requirements included the following:

- Operating rate of at least 100 stomachs per hour;
- Machine safety;
- Easy to clean;
- Semi-automated operation;
- High reliability and minimal maintenance.



Vibratory bowl feeder for rubber bungs used in the final bottling machine.

Background & Business Context

Barber's Pole worm (so called because of its red and white appearance) is a blood-sucking parasite that infects the gut of sheep and goats. It is a major limitation on sheep and goat raising in many countries and is devastating for individual farmers, especially as the worms have become resistant to many treatments.

Our client, Dr David Smith, a veterinary scientist at the Moredun Research Institute, an Edinburgh-based animal health charity owned by farmers, had spent the past 20 years developing a vaccine for Barber's Pole worm. He discovered that a vaccine could be made on a small-scale by grinding up the parasites. Having taken out a patent, he wanted to scale up this laboratory work. He spent 8 years unsuccessfully trying to synthesise the vaccine so that it could be commercialised. He discovered that it was theoretically possible to produce commercial volumes using his laboratory work-flow, but no production-scale equipment was available which could practically achieve this goal. If such

equipment could be designed, then it would enable Dr Smith to set up a new business to produce and sell the vaccine.

Barbervax® is the world's first vaccine for a worm parasite in any host, not just sheep. As the vaccine was so novel and had proven intractable to commercialisation by standard methods, at the time we started working on the project it was unknown whether it would be possible to produce Barbervax® at commercial scale. Moredun's veterinary scientists were also unsure how popular the vaccine would be with farmers, particularly as 5-6 doses are required during the summer season for it to be effective.

Design Solution

Dr Smith asked 4c to investigate whether we could design and build production-scale equipment. It needed to be able to extract the Barbers Pole worms from sheep's stomachs obtained from the abattoir and clean them so that they could be used by Dr Smith and his team to make the vaccine.
After considering the end-to-end production challenge, we identified requirements for three separate machines. One to cut the stomachs open, one to harvest the worms and one to bottle the vaccine into 250ml containers within a sterile environment at the end of the process.

Scope of Work

There were a considerable number of technical challenges to be overcome in order to design the three machines. We used an iterative design process involving extensive prototyping and testing in our workshop to quickly design and test potential solutions.
The first challenge in the 'worm harvester machine', named NemeSys, was finding a way to dislodge the worms from the sliced open stomachs and doing so extremely rapidly. The Australian abattoir removes and collects the stomachs at a rate of about 500 per hour. Our equipment did not need to operate this fast as the stomachs could be kept for many hours without degrading. Our design priority was quality of output, followed by speed, at least 100 stomachs per hour. We tried agitation and after prototypes involving bath tubs, gin and tonic bottles and washing machines we discovered that a modified cement mixer offered the perfect solution, not least because it could be purchased from the local DIY store near Wormvax's Australian site.

The 4c team engaged in iterative and collaborative design and prototyping involving our client Dr Smith (far left).

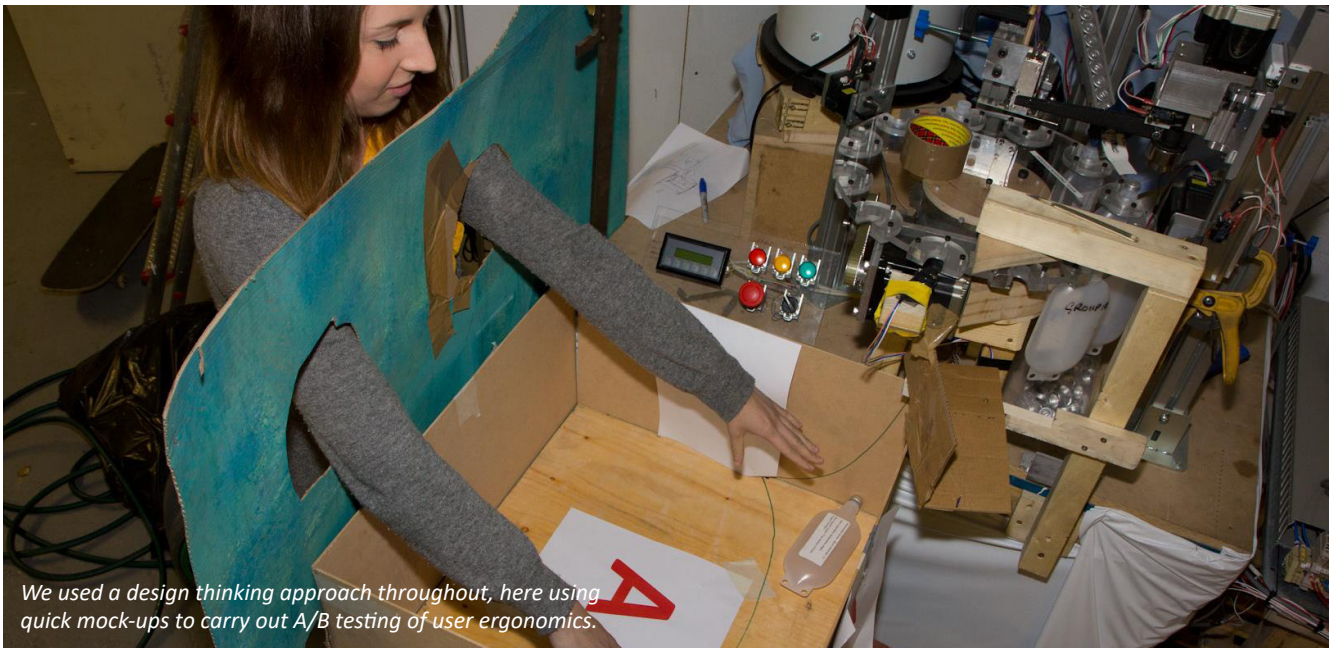
The stomach contents then had to be tipped onto a mesh to catch the worms. Again, through experimenting and coming at the problem with a 'fresh eyes' approach, we investigated various materials from fishing nets to fish net tights until we discovered that a table tennis net did the job perfectly.

The filtered worms make their way along trays and as they naturally clump together in warm water, they can easily be picked out with forceps and placed in saline solution ready for the vaccine to be made.
Our design process was similarly iterative for the two other machines. Our prototypes were crude, but they quickly proved the concept and we created functional solutions for the three different machines required.

Once we had developed the proof of concept prototypes and proved the feasibility of our proposed solution, we worked with the Moredun scientists to define the design brief and requirements for the production machines incorporating safety features, IP65 rating and minimal maintenance requirements. We also developed smart monitoring and control systems for semi-automatic operation. The final production machines were built in 4c's workshop, then shipped to Australia where they were installed and commissioned by the 4c team.

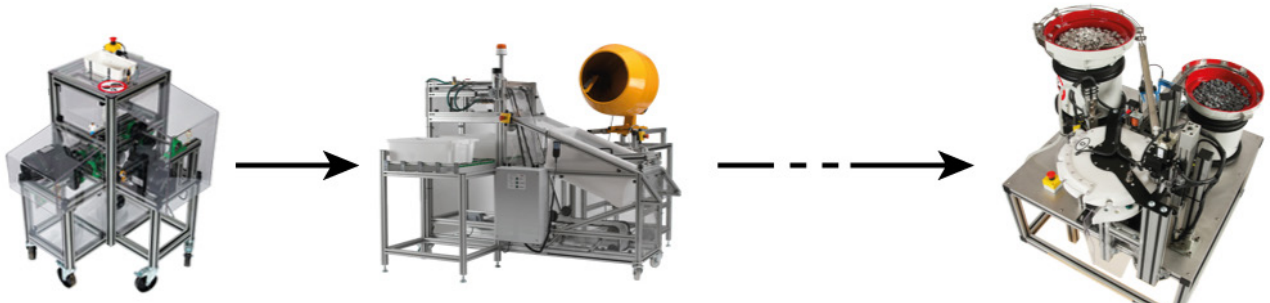
Market Overview

The Barber's Pole worm is prevalent in hot, humid climates across the globe. It affects millions of sheep, causing the death of entire flocks and devastating farming businesses. Australia is one of the countries worst affected. Our client says that gut worms cost the Australian sheep industry $450 million AUD annually, and that Barbers Pole worm is responsible for ¼ to ⅓ of this figure, $113m to $150m AUD. The Barber's Pole worm has developed high levels of resistance to drenching, which is the normal method of treatment.
Barbervax® is the first Barber's Pole worm vaccine available to



We used a design thinking approach throughout, here using quick mock-ups to carry out A/B testing of user ergonomics.

Our Design Solution for the Barbervax® Commercial Vaccine Production System



1. Abomasum (stomach) Slicer

2. NemeSys (worm harvester)

3. Bottling Machine

farmers. It is a world first, not only is it the first vaccine for the Barber's Pole worm, but it is the first vaccine for any worm parasite in any mammal host, including humans. Barbervax® offers a more sustainable form of control than drenching because it is extremely unlikely that vaccine resistant worms will develop. Like all vaccines, it works by stimulating the natural immune response of the animal.

Product Launch Date:
2014

Size of Design Budget:
£65,000 for the design of the three production machines.
Our total budget for design, build and commissioning was £200k.

Once Dr Smith succeeded in making Barbervax® in his lab, he began trying to synthesise it using molecular biology techniques. He expected that these techniques would enable him to develop a pharmaceutical formulation which he could patent and then license to an established pharmaceutical manufacturer. This is the normal method of commercialisation. After 8 years of trying to synthesise Barbervax®, progress was so slow that Dr Smith realised a completely different approach was needed. Barbervax® was initially launched in Australia. Barber's Pole worm is most commonly found in the Australian territories of New South Wales and Queensland, with combined sheep population of 28 million. The total sheep population of Australia is 67.5m.

The vaccine has also been launched in South Africa (24.5m) and there are plans to sell the product in New Zealand (27.6m) and the UK (33.3m) in the near future. The changing climate is causing an increase in Barber's Pole worm in some regions, including the UK.

Results

Summary

4c's design and development of commercial scale vaccine production equipment has enabled Dr Smith to achieve his original objective of producing the Barbervax® vaccine at commercial scale and making it avail-able to farmers to protect their sheep and their livelihoods from the deadly Barber's Pole worm parasite.

In the four years since Barbervax® was launched sales have grown rapidly from 300,000 to 2.5m. All doses of the vaccine have been produced by the machines designed and built by us. Around 500,000 sheep worth between $30 and $85m AUD were protected in 2017-18 from the Barber's Pole worm.

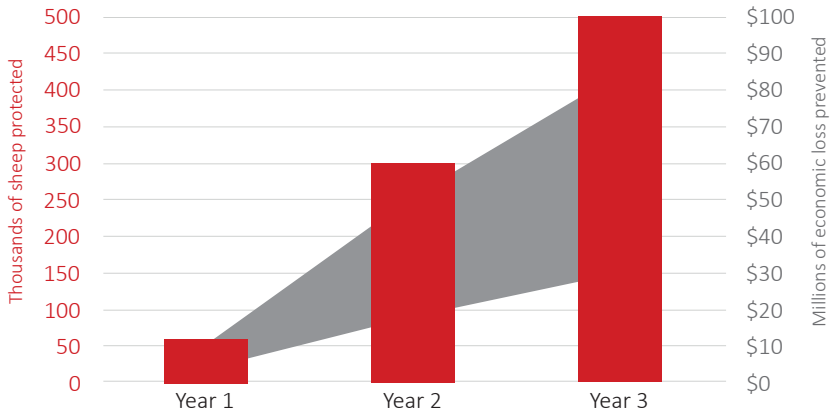
As a result of being able to demonstrate both the efficacy of the vaccine and the feasibility of producing it at commercial scale, Dr Smith and his team successfully raised over $1m AUD to set up a new business. Wormvax has created 8 new jobs, launched Barbervax® in Australia and South Africa with new markets planned for 2019 and is operating profitably, providing a return to its investors.
The production machines 4c designed have performed better than expected, according to our client, Dr Smith, "We are currently harvesting from 500 sheep stomachs in about 3 hours, yielding kilos of clean worms, figures which were unimaginable 5 years ago."

"We are currently harvesting from 500 sheep stomachs in about 3 hours, yielding kilos of clean worms, figures which were unimaginable 5 years ago."
Dr David Smith

NemeSys (worm harvester)

New Revenue Stream Created

The commercial scale production system designed by 4c has enabled the world's first vaccine for a parasitic gut worm to go on sale. As commercial scale production of the vaccine had proven intractable by normal pharmaceutical methods, our design input was crucial in enabling Dr Smith to start producing and selling the vaccine he had developed for the Barber's Pole worm.
Barbervax® was launched in 2014 in Australia with the vaccine produced and sold by Wormvax Australia. In 2016, the vaccine was registered and started selling under the trade-name Wirevax® in South Africa.
In the first years all 300,000 doses produced were sold out. Since then, production has grown rapidly year-on-year using the three machines designed and built by us: Year 2- 1.5m



Graph demonstrating the economic loss prevented by the use of the Barbervax® vaccine.

doses, Year 3- 2.5m doses. Wormvax estimate that over 500,000 sheep were vaccinated last year and so protected from the parasite. The value of each sheep ranges from $60 to $170 AUD per head, depending on the age and weight. Therefore, the potential economic loss to farmers prevented by the vaccine in the past year alone is between $30m and $85m AUD. The vaccine has been sold to approximately 200 farms to date.

"We were very pleased with the action of Barbervax® on our young sheep in this year. We have got through the spring, summer, and at least mid-autumn without the need to drench for nematode worms."
Barbervax® customer

Investment Raised

Demonstration of a commercially viable production method, along with scientific proof of the efficacy of the vaccine, enabled Dr Smith to raise over $1m AUD from Meat and Livestock Australia (MLA) and others to commercialise the vaccine.

Job Creation

Dr Smith and the Moredun Research Institute have set up subsidiary companies in three geographies- the UK, Australia and South Africa. The main subsidiary, Wormvax Australia, now operates a 5000-head sheep farm in Albany, Western Australia as well as producing and selling the vaccine. In Australia, 5 people are employed in manufacturing and 1 in sales. 2 people are employed by Wormvax in the UK, including our client Dr Smith. Due to the seasonality of the business all employees are part-time.

"Barber's pole is our single biggest challenge and we have resistance to a lot of drenches...It's a terrific breakthrough for our industry."
Barbervax® customer

Market Expansion

In the 4 years since market launch, Wormvax have expanded their Australian business, now 170 customers and have also entered the South African market where they have 30 customers. Sales are growing in both markets. A UK product launch is planned for 2019. New Zealand and wider European markets are expected to follow.

Return on Investment

Wormvax has generated operating profits of $750 AUD and is providing a return to the main investor, Meat and Livestock Australia (MLA) as well as royalties to the Moredun Research Institute.

Design Requirement	Result
Operating rate of at least 100 stomachs per hour	"We are currently harvesting from 500 sheep stomachs in about 3 hours, yielding kilos of clean worms, figures which were unimaginable 5 years ago." *Dr David Smith*
Machine safety	Meets UK and Australian regulations. Sharp, rotating blades were required in one of the machines so electrical cut-outs, emergency stops and extensive guarding were designed in.
Easy to clean	We designed to IP65 rating to enable the machines to be easily cleaned using water jets.
Semi-automated operation	A smart monitoring and control system was designed to enable semi-automatic operation.
High reliability and minimal maintenance	Simplicity and use of locally available parts was a key design principle. For instance, the use of a locally available model of cement mixer as the main agitation component in the NemeSys machine.

Exceeded Design Expectations

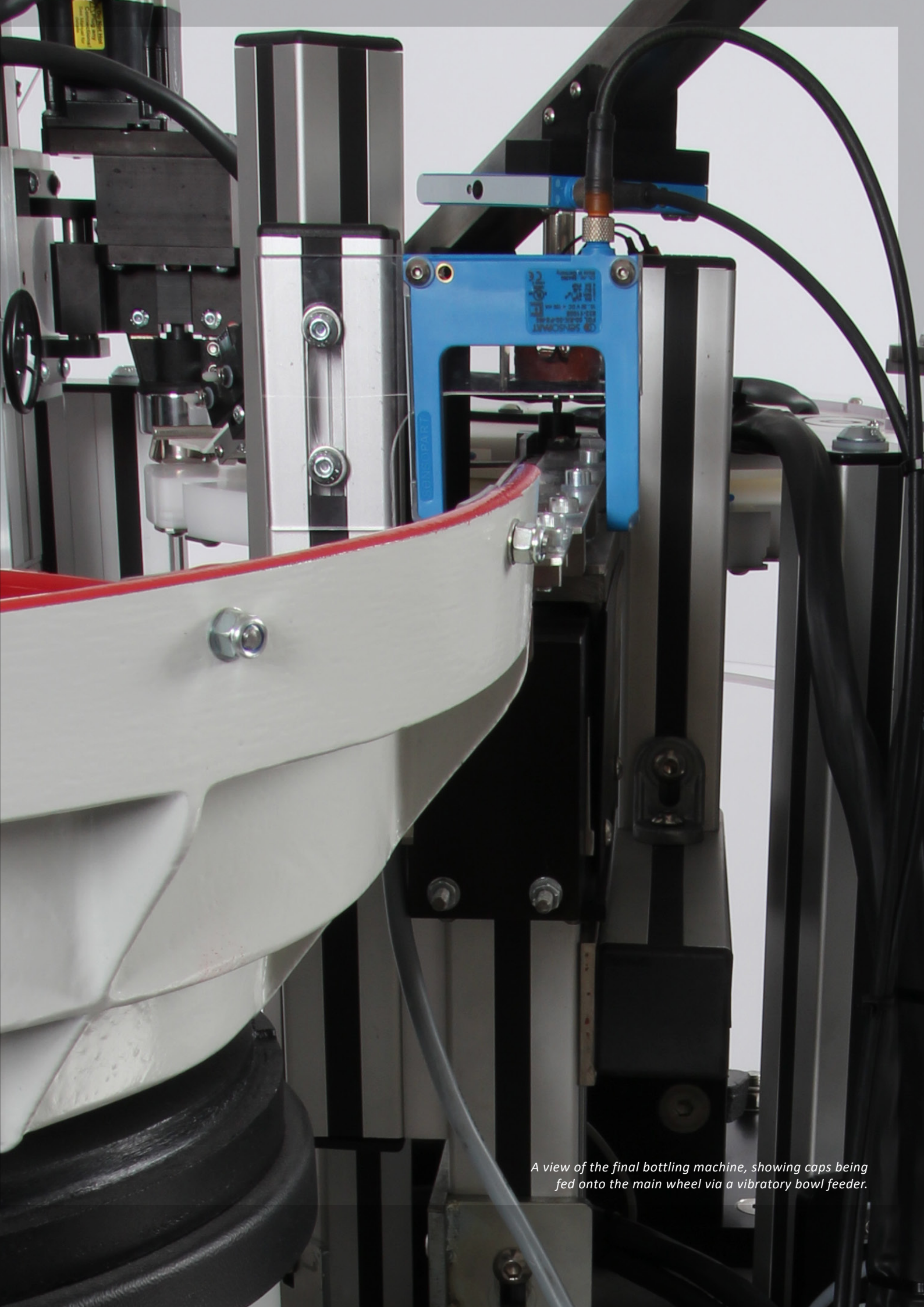
The three machines that 4c designed and built have now been operating for over 4 years and according to our client Dr Smith have performed better than expected.

Proof of Effect and Other Influencing Factors

It is clear that the efficacy of the vaccine is the most important factor in the rapid market uptake of this product. However, 4c's design input was crucial as the product would not have been able to reach the market without a commercially viable production system. Prior to our involvement, Dr Smith had spent 8 years trying a more conventional commercialization method using molecular biology, before asking 4c to investigate and design an alternative based on his laboratory work-flow.

4c were not involved in designing the marketing campaigns or communications which have raised awareness of the product in the target market. Wormvax employ a part-time sales person and have a website. They have advertised on Australia radio and displayed posters, banners and fliers at various agricultural and scientific meetings. They have not offered any price discounts or promotions to date. Several articles have been published about Barbervax® in the Australian press.

The 1m increase in sales figures from Year 2 to Year 3 belies reduced demand due to a drought in Year 3 in Wormvax's main market of New South Wales. As the parasite does not survive well in hot, dry conditions it was not such a problem as normal and farmers did not need to use as much vaccine. The increase in sales growth despite the drought reflects demand from new customers. Sales are expected to continue growing as the vaccine due to strong demand from new customers in existing and new market geographies. Climate change is causing an increase in Barber's Pole worm in some regions, including the UK, meaning that commercial scale production of Barbervax® is increasingly important for the well-being of animals and protection of farmers' livelihoods.



A view of the final bottling machine, showing caps being fed onto the main wheel via a vibratory bowl feeder.

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