

B1: Concept and objectives, progress beyond state-of-the-art, S/T methodology and work plan

B1.1 Concept and project objective(s)

PiedPiper is a simple concept, its “raison d’être” was to develop a safe, reliable pest control system aimed at rats which overcame the disadvantages of current systems and most importantly would use a toxin which will replace warfarin which is due to be banned by the EU in 2014 on Health and Safety grounds.

The PiedPiper Demonstration Action is the follow-on project from the successful *FP7-SME-2010-1 PiedPiper “Research for SMEs”* project (Grant Agreement Number 286852), which ends in November 2013. This has very convincingly researched, developed and proved the concept of the alternative Pest Control Device which is an entirely new approach to rodent control and utilizes a much safer toxin formulation than the current warfarin compounds. During the project it has become apparent that the PCD has applications for the control of species beyond the initial target group of rats, such as possums, grey squirrels and mongoose

When the REA announced that it had brought forward the filing date for the demonstrator grants we wondered if we would have enough data from the original PiedPiper project however we can confirm that the main challenge that we faced i.e. to kill rats with our cholecalciferol formulation (Vitamin D₃) has been successfully proven several months ahead of schedule. We thus feel confident that we can apply for the PiedPiper^{DA} Demonstrator Activity. There are two other aspects to the PiedPiper 1 project – the first being the screening of attractant molecules which is now underway and we will have results available by the commencement of PiedPiper^{DA}. The other aspect is the development of a pre-production prototype PCD (Pest Control Device). This has been completed and is due for delivery for testing by the end of November 2012.

To bridge the gap from the very successful PiedPiper research project, and enable its SMEs to address a significant market opportunity and growing market need, it is proposed that the PiedPiper Prototype will now be scaled up to **fully reliable operational commercial prototypes / preproduction unit**. It will then be demonstrated and validated over a 6-month period in trial work. This work will quantify the operational superiority of the PiedPiper prototype for the pest control industry, and will allow us to fully document the improvements in the results that can be obtained by using our PCD. We intend to publish a range of data including running costs, reliability, efficacy and a variety of other parameters required by the pest control industry.

There are a number of gaps to fill to take the PiedPiper project to market – hence this proposal for PiedPiper^{DA} which essentially fills the gaps between the PiedPiper technology being developed and the bringing of the technology and the overall PCD system to market. In order to do this there are five key elements to making this project a commercial success, which are:

- 1) A professional grade business plan to raise the 4 – 6 million Euros required to obtain registration, CE marking and place the product on to the EU market.
- 2) IP Protection work – this is to follow on from the IP protection due to be filed early in 2013.
- 3) Formulation of toxin and attractant into a commercially acceptable package

- 4) Using the information in item 3 to produce a commercial Pest Control Device, and carry out real world field trials
- 5) Market research and pre-marketing awareness of the technology promoting all the advantages of our PCD technology and the safe toxin formulations that have been developed.

Environmental Toxic Load (ETL)

This concept may be the **most overlooked aspect of pest control and the use of toxins in the environment today**. ETL needs to be explained and promoted to regulators, the pest control industry and the public as it is the **key to safer pest control** by outlining the problems caused by and risks of the usage of the current toxins. It may seem strange but the PiedPiper project spent its time developing the formulations for our rodenticides and it was only after looking through some notes dating back to 2008, we realized how significant our approach is with regard to ETL. In New Zealand one of the primary concerns is how much toxin by weight is needed to put into that environment to achieve the desired effect and what is the downside risk of free toxin in the environment. In addition to the actual operation of the new PiedPiper PCD, the project will quantify the market and identify potential users of a commercial PiedPiper PCD system with a great emphasis on **safety of the technology compared to other toxins**. We will also demonstrate to the industry how the use of our PiedPiper PCD can reduce the amount of toxins in the environment. Currently we are allowing tonnes of warfarin based toxins to be placed in the environment without any real consideration of the consequences. The aim is to kill rats **but at what cost?** Tonnes of environmentally toxic compounds to kill rats and mice are placed in bait stations, heaped into plastic trays in buildings or incorporated into food blocks and they all have one factor in common – **none of them are secure from other animals or humans, which creates a risk of accidental poisoning**. Warfarin is very soluble and thus prone to being dissolved resulting in the contamination of water sources. The PiedPiper PCD is secure as the toxin is enclosed and utilizes a toxin that has a fraction of the toxicity to humans, pets and birds of prey that warfarin's possess. Using a single shot, the PiedPiper PCD delivers a small quantity of toxic spray from an aerosol can on to the back of the rodent (1ml dose for rats). Within 15 minutes it is absorbed through the dermis and into the blood stream.

Indeed, the original PiedPiper proposal was based on delivering 5 ml in 0.2 of a second using a high pressure aerosol and a full galleried valve - (eg Mister Muscle drain cleaner can deliver 250 ml in 5 seconds). Indeed, Summit Europe, who are number 2 in the world in aerosol valve technology, joined the PiedPiper consortium as they thought it was possible to produce a valve to deliver 5 ml in 0.2 of a second. The situation today is that we have gone down in volume from 5 ml to a 1 ml dose in 0.2 of a second - this is easily attainable with standard existing valve technology. PiedPiper is based on dermal disruption, which have been extensively studied in vivo and in vitro studies during the original PiedPiper project performed at Aston on a broad range of solvents and concentrations, whereby the ultimate test is 1 ml of product on the back of rats (with standard coats) and the result was death in 48 hours max.

The environmental load is virtually zero – it is a small quantity that is readily absorbed through the skin in minutes. In terms of kill, rats can take their body weight of warfarin laced block to be killed (average 400gm) compared to our 1ml of spray weighing around 1 gram in weight. This means we are around **0.25% of the toxic load compared to a single kill of warfarin**. There is an additional benefit to the PiedPiper PCD technology which is a single shot approach i.e. one spray = 1 kill. Warfarin's are multi-feed and do not always cause death as they rely on a cumulative dose. Some rats are killed but many do not eat enough to cause death and **develop tolerance to the warfarin**. This is supported by the scientifically documented reports for example: **The biochemistry of warfarin resistance in the rat**. R J Davis and B H Davies Biochem J. 1970 July; 118(3): 44P–45P and A molecular mechanism for genetic warfarin resistance in the rat REIDAR WALLIN, SUSAN M. HUTSON, DEAN CAIN, ANDREW SWEATT and DAVID C. SANE. The Journal of the Federation of American Societies for Experimental Biology. vol. 15 no. 13 2542-2544.

Warfarin toxins in the environment are about as close as you can get to playing environmental Russian roulette without breaking the law.

One of the big issues with regard to raising funding from investors is that of IP protection for the invention or development. PiedPiper will be no exception to this situation. All investors these days ask for IP protection documentation and this normally means patents and registered designs.

The PiedPiper project will have IP filed as an initial application early in 2013 either in the UK or Ireland, and then we will move on to register in other countries across the EU. As this is a global product we will also need to file detailed country specific applications for countries such as the USA, New Zealand, Australia and Canada. We already have interest in the technology from the USA and New Zealand.

There is a need for an improved Pest Control in the EU and globally.

Production of a professional safe and cost effective method for rodent control.

To achieve this we need to be able to carry out the following work as part of the Demonstrator Activity.

- 1) We have 4 formulae to kill rats – what we need to do now is formulate a commercial package – utilizing the knowledge of AJI Technology and the testing facilities of Cellvax-Pharma.
- 2) We need to develop a strategy to protect the IP, which covers: The PCD design the dermal penetrant and toxin formulation and some of the testing protocols we developed during the project.
- 3) A final precompetitive prototype needs to be developed by IRIS with the input of all SME partners so we are market ready.
- 4) One of the most important issues will be the development of the business plan to raise the funds to enable exploitation of the PiedPiper PCD technology.

The EU's announcement to **restrict the availability of warfarins to the pest control sector from 2014** has focused the minds of the entire industry worldwide. In global terms the EU market is around a third of the global market for pest control. Based on feedback from the field trials the project will disseminate the PiedPiper PCD system information to potential users and business partners through various media and specific events, and will develop and validate a Business Plan for

the SMEs to commercially develop and exploit the system in the market after this Demonstration Project ends.

Scientific and Technical Objectives of PiedPiper^{DA}.

In light of the above, and in an attempt to gain a competitive edge in the marketplace, the original PiedPiper project identified a real need to provide SMEs operating within the European pest control sector with a viable solution to an increasing problem. It took a total change in approach to come up with a methodology that worked reliably. As such, the original PiedPiper project successfully developed and validated to pre-competitive scale a Pest control device with three key features:

- a) New Toxin,
- b) New means of attracting rodents,
- c) New delivery system.

PIED-PIPER^{DA} now proposes to fulfil the following objectives through this Demonstration Activity Project:

- 1- to perform a market analysis for the EU and global pest markets and the applications where the PiedPiper Pest Control Device would fit
- 2- to perform hardening of the PIEDPIPER prototype from the original project in order to get it ready for further demonstration work
- 3- to organise demonstration pilots and validation works towards regulatory compliance
- 4- to draw up a business plan, as well as commercialisation plans for demonstration
- 5- to build on the knowledge management and IP protection strategy and to disseminate the PiedPiper PCD to the market and stakeholders.

B.1.2 Progress beyond the state-of-the-art

To say there was a state of the art is over complementary to the pest control industry – the current “technologies” used to kill rodents (rats and mice) involve a number of bizarre trap systems such as the Danish trap that works in sewers. It stands vertically and has a trigger mechanism in it – when the rat triggers the system steel knives come down and skewer the rat. The knives remain there for 20 minutes before retracting. The sewerage water then washes away the dead carcass. Another system involves a box with bait in it that electrocutes the rat. There are also captive bolt systems and snap traps – all of them are time consuming and expensive (with the exception of the simple little nipper snap trap).

The above is about as sophisticated as pest control gets however the widest used control mechanism these days is warfarin based poisons. One could also argue that it is also the most unsophisticated system. These toxins have been around for 60 years or so and due to the fact that they were inherently unsuitable for use as rodenticides. The biggest cause of our current problems is

that the poisons were not suitable for a single treatment. They were based on a principle of multi-feeding, i.e. a cumulative ingestion of poison that eventually causes death. Unfortunately this has resulted in warfarin tolerant rats. There are also the issues of secondary kills – dogs, cats and birds of prey from ingestion of poisoned rat carcasses. Add to this that not one of them can comply with the EU Biocide Directive (Julie Girling, MEP and EU Biocide Directive committee). Add to this the already announced EU wide ban on warfarins from 2014 and you can see that the current state of the art is no competition to our novel and innovative approach.

The European Pest Control Industry is made up of a spread of both large and small companies, of which 99% are SMEs. The rodent control sector is worth some €3.75 billion, annually within the EU and in excess of €10 billion globally. The need for control of rats can be split into three categories:

- 1) Disease risk to humans – Rats are responsible for the spread of over 60 diseases to mankind. This includes diseases like bubonic plague and leptospirosis.
- 2) Damage to and consumption of food crops. Contamination of food and water supplies.
- 3) Damage to infrastructure – gnawing through items such as wires, timber supports and water pipes.

The picture further afield is much worse – in countries like India where pest control is less sophisticated it is estimated by UN FAO that **40 % of all agricultural crops are contaminated or damaged by rodents** (the majority being rats).

New Delhi airport has had to be fully rewired as the rats damaged all of the cable installations.

Australia – grain stores get invaded by millions of rodents which eat and contaminate the grain with drastic economic damage.

Pick up virtually any mainstream daily newspaper globally and it is almost certain that there will be articles about rats and their increasing threats to humans. To be fair in a sense it is not all the rodents fault. We in the West have basically become banquet providers on a daily basis with all the food that is wasted and discarded from our fast food outlets and supermarkets (as a result of out of date product). To make matters worse we have fed the rats and mice with an exotic cocktail of poisons in such a way that **they are not guaranteed to consume a lethal dose**. The result of this exotically called multi-feed approach to poisoning is that those animals that do not consume a lethal dose **they can become tolerant to these toxins**. This gives the newspapers further grounds for copy – “poison tolerant rats”, “rats as big as cats”, “super rats” it has become a never ending source of stories on slow news days.

The reason we decide to develop a new pest control device was that it was clear that the current system was not working and that not just human health but our entire eco-structure was at risk.

The problems we set out to address were as follows:

- 1) **Removal of the risks of tolerances being built up in rodents.** The currently used warfarin derived toxins were developed after the Second World War when safety trials were not required. A number of compounds proliferated over the years 1947 to the late 50's as each large chemical company produced its own compound with a slightly different formulation. The reason for this was so that each company could claim that their product was better than the competitors. This was

effectively the only differentiation point in the market place. All of the compounds were lethal to rodents and all other animals. However in this post war period environmental issues were not even considered as a factor. In the 60's and 70's environmental issues became more important and a number of papers were published suggesting that tolerance in rodents was a possibility. As we moved into the 80's and onwards scientific research proved unequivocally that tolerance to these toxins was in fact a reality in both rats and mice. These products have been on the market for 60 plus years and now pose a greater risk to mankind, birds, animals and the environment than they did when they were first invented. It is certain that there are now highly tolerant rodents living freely in our towns, villages and cities. They are known to **transmit 60+ diseases to mankind many of which could trigger epidemics**. We have created a dream environment for these rodents – they can now dine out on a feast of takeaways from all manner of exotic country cuisines or if the weather is inclement they can in many cases dine in. To put it as clearly as we can – our society is taking an unreasonable and uncalculated risk by not controlling rodents more effectively. What we need to do is to look at ways of bringing the rodent numbers under control as quickly as possible with a safe toxin which will not exasperate the situation but will guarantee by virtue of its formulation not to cause further tolerance issues. This matter is of such concern that a number of monitoring bodies have been set up across Europe. In the UK NAPA - the National Pest Association has a monitoring group called RRAG – Rodent Resistant Action Group.

- 2) **Recognition that the current toxins were not safe in the environment** – deaths in cats, dogs and birds of prey are all well documented. There are also several cases of **children and adults being poisoned by warfarin based toxins** – in these days of stringent health and safety regulations their toxicity to secondary animals, birds, humans and aquatic ecosystems is just no longer acceptable and **they need to be withdrawn**. Everyone except the chemical companies agrees with this but we have to have a viable product or system to replace them with. The EU has given a **date of 2014 for withdrawal** from the market and the chemical industries are lobbying hard to get extensions and continuation agreements despite them knowing the risks and damage their products are doing to the environment and potentially risking human epidemics with disease transmission from rats / mice that these toxins can no longer kill. The bottom-line is these products are old and unsafe and are only on the market by default of age and grandfather clauses. This is PiedPiper's primary goal to make the environment safer and get us back to being in control of pest eradication.
- 3) **Stop the risks associated with multi-feeding** and replace it with a single shot approach with a toxin that is safer to other species than the current toxins. PiedPiper's technology works on the fact that rats are super sensitive to our toxin formulation. Due to our delivery system it is virtually impossible for other animals to be exposed to our toxin directly. As is well documented a lot of animals and birds that dies with toxicity to the warfarin type compounds do so because they have ingested carcasses of poisoned rats. The reason that this has happened is that these products never were capable of a single feed kill so to make them work there had to be a number of ingestions of the toxin i.e. multi-feeds. Multi-feeding was the cause or trigger that gave rise to increase tolerance to these toxins. Rats and mice also found more food to consume that was not poisoned and hence the gap between doses could increase and the ability of the rats / mice to process the toxin increased. Ultimately they became **resistant to the toxins**. The use of these multi-feed toxins is no longer acceptable – it

is an accident waiting to happen. We need to move to a single shot approach – **one treatment = one death.**

- 4) **Develop a professional delivery system that guarantees a lethal shot each** and every time. This concept led to the development of the PCD (Pest Control Device). We asked a simple question what the best way to kill a rat is. Answer – single dose. How do you get the rat to the PCD? Answer by attracting it either with a food odour or to use an attractant smell. The PiedPiper PCD works by the rat smelling the attractant and entering the PCD, which triggers a LED to prime the toxin spraying system, as it moves further through it triggers another LED and gets sprayed with our formulation of cholecalciferol and dermal penetrant. The rat leaves the PCD and **dies within 48 hours.**
- 5) **Adopt an Environmentally friendly approach to the problem** – To explain why cholecalciferol was chosen as the toxin would take a considerable period of time and all we can do here is touch on some of the reasons – rats are supersensitive to vitamin D₃ compared to humans, cats, dogs and birds of prey. This is related to them being nocturnal and their livers not being able to process vitamin D₃. Cholecalciferol was pre warfarin used for rodent control it fell out of fashion as the big chemical companies wanted to promote their unique molecules of warfarin based products. The fact that we could make a multi-shot aerosol driven device with only a single shot being required to cause a kill was important – both from a pest control point of view and also from a safety to the environment point of view.
- 6) **Cut down the cost per kill by being more effective** – The less attention from operatives that a pest control system needs then the more efficient that system is and the lower the cost of each kill. Less visits by virtue of our large dose numbers per canister further contribute to this efficiency as does not involve having to clear out & re-bait traps.
- 7) **Cut down on the Environmental Toxic Load (ETL)**, i.e. the total amount of toxin in the environment, and thus reduces damage to the environment and rats themselves. We have asked this question of industry consultants, pest control operators, the pest control trade bodies and health and safety regulators. How much warfarin based toxin is used in the EU? No one has an answer but it makes sense to conclude that from the chemical company's point of view the more the better as it creates fatter profits. The PiedPiper system will introduce a fraction of the weight of toxin to the environment that the warfarins do and it will be at non-toxic levels where ever it occurs. Our system effectively transfers toxin to the rat in 0.2 seconds. It then takes a few minutes to absorb through the skin and then the levels build in the bloodstream – resulting in death within 48 hours. The carcasses do not pose a risk in terms of secondary kills, i.e. they will not kill animals or birds that ingest them. The New Zealand government have spotted this ETL as a risk factor and are working to reduce it where ever possible.
- 8) **Cut down on labour and transport costs by making the pest control systems more efficient** as there will be a lot less toxin consumed – every dose in our PCD will be an effective dose. In these days of high labour and higher fuel costs we need to reduce the number of times that a site visit is required. We will aim to incorporate an “I need refilling” alert system to our PCD's when they go to market. Our product will be a plug and play aerosol system – no fiddling with placing toxic bait blocks around a site, no pouring of bait toxin into plastic trays – again we will save time and thus reduce costs.

- 9) **Utilize a compound to which rats and mice are sensitive to**, yet to other species it is just a therapeutic dose. This was a primary reason why we decided to use cholecalciferol – Vitamin D₃ There is an enormous amount known about the use of vitamin D₃ in humans from neonates to geriatrics. **It is very safe!**
- 10) **Aquatic environments** – warfarins being very soluble they can cause significant damage if they get dissolved into water and then enter into aquatic ecosystems.
- 11) **We can kill warfarin resistant rats with our PCD and cholecalciferol toxin formulation!** Let me ask a simple question – by whom and how else can this be achieved? We have had 60+ years of warfarin toxins in the pest control industry – all of these products supplied and promoted by the big chemical companies. The effect to our environment is not unlike the DDT scandal of the 1960's we have created millions of potential monster resistant rats???
- 12) **Other Environmental issues addressed by our PCD** in terms of materials and construction The PiedPiper PCD is to be constructed of recycled recyclable plastics to minimize environmental impact and reduce carbon footprint to minimal levels. Additionally we will be using standard recyclable mild steel cans for our toxin propellant and all packaging materials will be recyclable.