



**Biocontrol Limited**

**The Biological Answer to  
Antibiotic Resistance**



## ***The Biological Answer to Antibiotic Resistance***

**Biocontrol Limited** is developing safe, specific, effective and adaptable biological agents, targeted at markets where current chemical drugs are failing or ineffective. As a result, there is significant unmet clinical need for its products.

Having completed phase 1/2 clinical trials of its lead product, BioPhage-PA, the company is now moving into phase 3 trials. Additional product trials are planned.

BioPhage-PA is intended to control bacterial infections with *Pseudomonas aeruginosa* using bacteriophages, naturally occurring viruses that target and destroy bacteria. These are capable of destroying bacteria that are highly resistant to chemical antibiotics, and can also penetrate and destroy bacterial biofilms.

Biocontrol has:

- A lead product that has successfully completed phase 2 clinical trials, with strong commercial prospects
- World-class scientific expertise
- A strong portfolio of intellectual property based around multiple patent applications with the potential for orphan drug approvals
- An experienced and highly entrepreneurial business team
- Outstanding business opportunities in large, expanding and poorly served markets

The current development streams establish Biocontrol as the market-leading company in the expanding field of bacteriophage-based therapeutics.

Chemical agents have served well, but are failing. They are far more damaging than was at first realised, and resistance is a huge and increasing problem. In summary:

**Life Adapts**

**Chemicals Do Not**

**A new approach is needed**

**Biocontrol is providing that approach**

## THE ANTIBIOTIC CRISIS

Chemical antibiotics were one of the great health successes of the 20th century, and the "antibiotic age" has changed public expectations about the results of infectious disease. However, it has also seen high levels of inappropriate prescribing that, along with uses in agriculture and elsewhere, have contributed to the increasing problem of antibiotic-resistant bacterial infections.

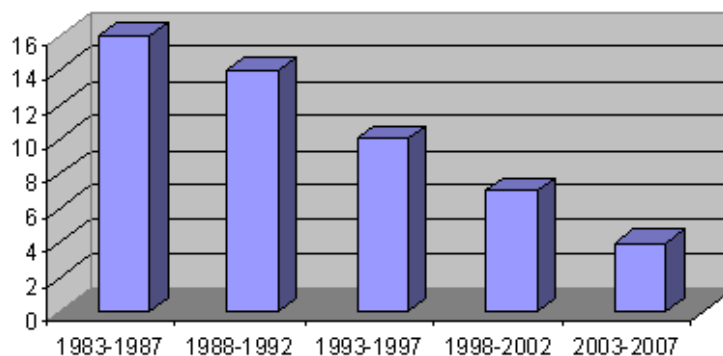
The term "superbug" has entered the common vocabulary for multidrug-resistant bacteria such as vancomycin-resistant Enterococcus (VRE), multidrug-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant *Pseudomonas aeruginosa* (MRPA). More recently, the term "XDR" has been introduced to describe bacteria that are beyond all effective antibiotic therapy.

Interest within the pharmaceutical industry was focused for many years on other areas of development, meaning that the pipeline of new antibiotics has almost dried up. Only three new classes of antibiotics (lipopeptides, oxazolidinones, and streptogramins) have entered the market in the last four decades.

However, new chemical antibiotics do not seem to be the answer. Zyvox provides a worrying example. It is the first of the oxazolidinones, hailed as the first new class of antibiotics for thirty years.

Development took fourteen years from the first laboratory work to licensing for use.

FDA approvals for new antibiotics



Resistant bacteria appeared in the clinic within one year.

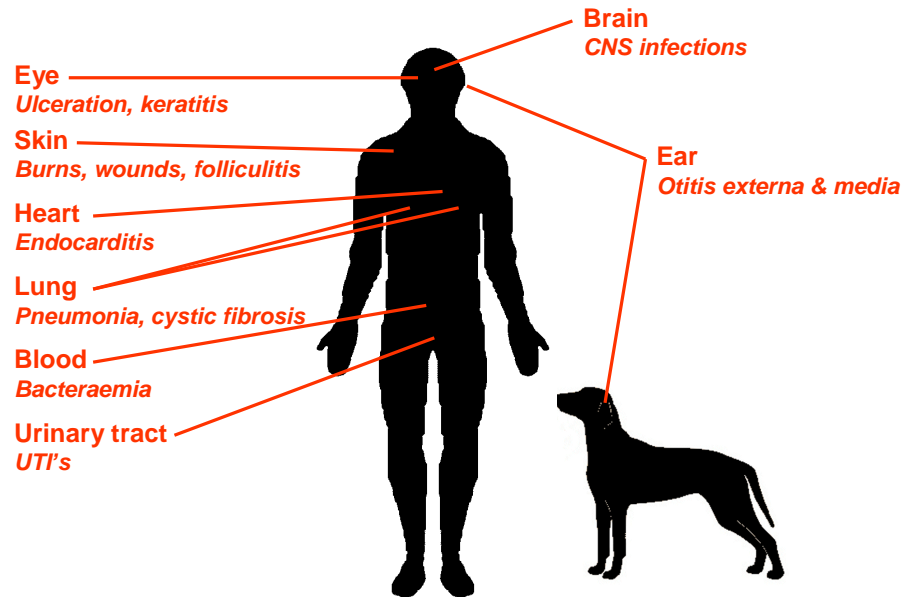
Resistance now develops faster than new antibiotics can be produced, evaluated and processed through regulatory approvals.

Additionally, it is important to discriminate between susceptibility to a particular antibiotic in the laboratory and the efficacy of that antibiotic in the patient. In particular, bacteria that grow in the complex structures known as biofilms may be highly resistant to antibiotics, even when laboratory assays show apparent sensitivity.

This is particularly true for Biocontrol's initial target, *Pseudomonas aeruginosa*.

## PSEUDOMONAS AERUGINOSA AND HUMAN INFECTION

### Sites of infection by *Pseudomonas aeruginosa*



*Pseudomonas aeruginosa* is a common soil bacterium, with a liking for damaged human tissue. It is highly resistant to antibiotics, both at the genetic level and as a result of living in complex, multilayered biofilms.

Over five million cases of clinically significant human infection are reported each year in Europe, North America, and Japan, with health spend of over £2 billion *per annum*.

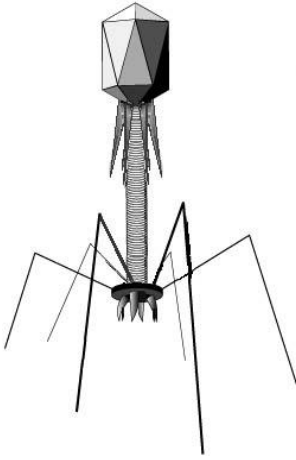
Antibiotic resistance has always been a serious problem in the treatment of *Pseudomonas* infections, and new multiple-resistance genes are still appearing.

For example, 80% of adult CF sufferers have chronic *Pseudomonas aeruginosa* infections of their lungs, and this is the main cause of death among CF sufferers.

Dr. Kenneth Todar, writing in 2004, noted that “The futility of treating *Pseudomonas* infections with antibiotics is most dramatically illustrated in cystic fibrosis patients, virtually all of whom eventually become infected with a strain that is so resistant that it cannot be treated”

Biocontrol's lead product is based on more than 15 years of research on bacteriophage-based control of *Pseudomonas aeruginosa* infections.

## THE NATURE OF BACTERIOPHAGES



Bacteriophages ("eaters of bacteria", often known simply as "phages") are naturally occurring viruses that infect bacteria.

It is estimated that the total number of bacteriophages on Earth exceeds ten thousand billion billion billion ( $10^{31}$ ), making them the most numerous form of life.

Humans and all other forms of life are continually exposed to a rich and ever-changing bacteriophage ecosystem, but because they only infect bacteria we simply do not see this happening around us.

Even among their bacterial hosts, bacteriophages are highly specific, with most infecting only a single species of bacteria. In many cases, only specific strains within that species are infected.

More than 90% of bacteriophages have a head containing the double-stranded DNA genome, extending from which is a tail through which the DNA can flow into the target bacterial cell. This tail can be long or short, flexible or stiff, and is a key characteristic of the different families of bacteriophages. Fibres at the end of the tail find specific receptors on the surface of target bacteria.

Once the bacteriophage has infected the host cell, the resultant infection may be either lytic, reprogramming and soon destroying the infected cell or lysogenic, where the phage genome is integrated into the bacterial genome and passed on to the next generations of bacteria.

A typical lytic bacteriophage will produce 100-300 new bacteriophages from an infected bacterial cell in a matter of hours. These can then go on to infect and kill a whole new generation of the target bacteria.

This exponential replication only stops when the bacteriophages run out of target bacteria. Then, they cannot grow any more. Without their target, they are simply small masses of protein, to be removed by the normal clearance processes of the body.

## **BACTERIOPHAGES AS THERAPEUTIC AGENTS**

Bacteriophages were first discovered in 1915, and were then shown to kill bacteria taken from patients suffering from dysentery. Felix d'Herelle, a pioneer of this work, noted that bacteriophage numbers rose as patients recovered and suggested that the two were linked. Following this, d'Herelle was an early pioneer of what became known as bacteriophage therapy.

Up until the discovery of effective antibiotics, bacteriophages remained a real alternative to existing therapies. When broad spectrum antibiotics came into common use, bacteriophages were seen as unnecessary, with antibiotics being seen for many years as "the answer" to bacterial disease. This attitude persisted until the development of the wide-ranging (and in some cases total) resistance to antibiotics seen within the last ten years. In many cases it is necessary to use expensive new antibiotics (such as Zyvox for *Staphylococcus aureus*) or "drugs of last resort" (such as Vancomycin, again for *Staphylococcus aureus*) which often require complex routes of administration and can have toxic side effects, necessitating prolonged hospital treatment. Even to these drugs, resistance is reaching worrying levels.

In the light of current knowledge, it is apparent that early work with bacteriophages was hindered by many factors. One of the most significant was the widespread belief that there was only one type of bacteriophage, a non-specific agent that killed all bacteria. This was wrong. In fact, the exquisite specificity of bacteriophages is one of their main strengths. In addition, poor understanding of the causes of disease led to exaggerated claims that damaged the reputation of bacteriophage therapy.

With the far greater understanding of bacteriophages and their function that is now available, it is possible to identify the bacteria which are causing disease and then target them with bacteriophages that will kill those bacteria, and only those bacteria. This specificity has other benefits. Whereas antibiotics can kill a wide range of bacteria, leading to recolonisation of the body by inappropriate and often harmful bacteria, bacteriophages selectively eliminate only the target.

This combination of potency, safety and specificity underlies the recent resurgence of interest in this field.

## CLINICAL TRIALS

In 2004, Biocontrol successfully completed a veterinary field trial of its bacteriophage mixture against chronic *Pseudomonas aeruginosa* infection of the canine ear. This was the first clinical trial of a bacteriophage therapeutic against its target infection to be conducted to modern standards. The trial investigated the treatment of dogs with severe ear infections caused predominantly or solely by *Pseudomonas aeruginosa* which had resisted clearance with repeated courses of conventional antibiotics. One dose of the bacteriophage mixture was administered with post-treatment monitoring at two to four days after treatment.

This study demonstrated a significant reduction in bacterial load within two days (mean 63%; range 29% to 97%):

This improvement was reflected in a reduction of mean scores for all individual clinical indicators (occlusion, erythema, ulceration, discharge amount, discharge type, odour) within two days for all indicators measured. The aggregated clinical score improved within two days in all cases

Monitoring of both local and systemic pro-inflammatory indicators indicated no localised or systemic inflammatory responses. Bacteriophage multiplication was also observed in all cases, confirming bacteriophage activity in the presence of the bacterial target

This study confirmed that the bacteriophage formulation tested was effective against a mature, antibiotic-refractory *Pseudomonas aeruginosa* infections in the clinical setting.

Following the successful veterinary trial, regulatory and ethical permission was obtained for a Phase 1/2 clinical trial at a specialist hospital in Central London, targeting infections of the human ear.

Mild human infections of the outer ear (*otitis externa*, known as "swimmer's ear") are common. However, if the infections become chronic, more severe disease can result. *Pseudomonas aeruginosa* is a major cause of these infections as well as of infections of the middle ear (*otitis media*).

In diabetics, malignant *otitis externa* and *otitis media* can occur and these can be life-threatening. 1.25% of the population is affected by otitis every year, and of these 3% are referred to secondary care at specialist ear, nose and throat (ENT) centres. Treatment of severe or chronic *otitis* often requires the use of aminoglycoside antibiotics which may be ineffective and cause damage to hearing.

The outcomes of Biocontrol's phase 1/2 trial targeting these severe chronic infections were reported in a peer-reviewed paper in the August 2009 edition of the specialist journal *Clinical Otolaryngology*:

## A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy

Wright, A., Hawkins, C.H., Änggård, E.E. & Harper, D.R.

**Clin. Otolaryngol.** 2009, 34, 349–357

**Objectives:** To evaluate the efficacy and safety of a therapeutic bacteriophage preparation (Biophage-PA) targeting antibiotic-resistant *Pseudomonas aeruginosa* in chronic otitis.

**Design:** Randomised, double-blind, placebo-controlled Phase I/II clinical trial approved by UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Central Office for Research Ethics Committees (COREC) ethical review process.

**Setting:** A single specialist university hospital.

**Participants:** 24 patients with chronic otitis with a duration of several years (2–58). Each patient had, at the time of entry to the trial, an ear infection because of an antibiotic-resistant *P. aeruginosa* strain sensitive to one or more of the six phages present in Biophage-PA. Participants were randomised in two groups of 12 treated with either a single dose of Biophage-PA or placebo and followed up at 7, 21 and 42 days after treatment by the same otologist.

Ears were thoroughly cleaned on each occasion and clinical and microbiological indicators measured.

**Main outcome measures:** Physician assessed erythema/inflammation, ulceration/granulation/polyps, discharge quantity, discharge type and odour using a Visual Analogue Scale (VAS). Patients reported discomfort, itchiness, wetness and smell also using a VAS. Bacterial levels of *P. aeruginosa* and phage counts from swabs were measured initially and at follow-up. At each visit patients were asked about side effects using a structured form. Digital otoscopic images were obtained on days 0 and 42 for illustrative purposes only.

**Results:** Relative to day 0, pooled patient- and physician-reported clinical indicators improved for the phage treated group relative to the placebo group. Variation from baseline levels was statistically significant for combined data from all clinic days only for the phage treated group. Variation from baseline levels was statistically significant for the majority of the patient assessed clinical indicators only for the phage treated group. *P. aeruginosa* counts were significantly lower only in the phage treated group. No treatment related adverse event was reported.

**Conclusion:** The first controlled clinical trial of a therapeutic bacteriophage preparation showed efficacy and safety in chronic otitis because of chemo-resistant *P. aeruginosa*.

Bacteriophages also appeared to reduce levels of antibiotic resistance in infecting *Pseudomonas aeruginosa*, suggesting the potential for useful combination effects. A patent filing has been submitted based on these findings.

Biocontrol holds a portfolio of granted and submitted patent applications, both licensed and filed by the company. Together with the potential for orphan drug applications, the company considers that these will underpin its plans for the commercial development of a range of bacteriophage-based therapeutics.

Following the completion of this initial trial, the company has received positive advice from the Scientific Advice Working Party of the European Medicines Agency, and from the Center for Biologicals Evaluation and Research of the US Food and Drug Administration at a pre-IND meeting. The advice received indicates the sufficiency of work to date to support further progress for a range of infections, and the company is now working to progress BioPhage-PA into phase 3 trials against *otitis* and into trials against *Pseudomonas aeruginosa* infected leg ulcers. These are intended to support uses in a range of hospital-acquired infections.

*Pseudomonas aeruginosa* accounts for more than 10% of all hospital-acquired infections, and this is an area with high levels of unmet clinical need. Biocontrol's bacteriophage-based therapeutic is proposed initially to be used for topical applications, such as those of the skin and surgical wounds, which account for approximately one quarter of hospital-acquired infections. *Pseudomonas* is a particular problem in patients with severe burns.

In addition, a novel therapeutic, BioPhage-PR, has been developed for use against respiratory infections caused by *Pseudomonas aeruginosa*.

*Pseudomonas aeruginosa* is the leading killer of adults with cystic fibrosis (CF) and is a serious health concern for all sufferers. This represents a very significant potential use for a bacteriophage-based therapy. Treatment with aerosolized antibiotics can moderate, but cannot clear, the infection. It is anticipated that trials in this area will be undertaken with financial and technical support from the US Cystic Fibrosis Foundation.

There is a clear and increasing unmet clinical need for new approaches to the control of *Pseudomonas aeruginosa* infections, and beyond that for the control of other antibiotic-resistant bacterial infections. Biocontrol is leading the development of bacteriophage technology as a novel approach in this field.

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**A new approach is needed**

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## CONTACT DETAILS

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### **Inlicensing:**

Biocontrol is interested in working with partners from all sectors. If you have a bacteriophage-based technology that you feel might be of interest to the company then please contact Dr. David Harper, Chief Scientific Officer

[david.harper@biocontrol-ltd.com](mailto:david.harper@biocontrol-ltd.com)

### **Outlicensing:**

Biocontrol is currently seeking licensing partners to develop specific technologies within its portfolio. If you are interested in discussing licensing opportunities then please contact David Scott, Commercial Director

[david.scott@biocontrol-ltd.com](mailto:david.scott@biocontrol-ltd.com)

### **Investor contacts:**

All investor contacts are handled by Mr. Patrick Benham-Crosswell at BC Capital, the financial advisors to the company. Further information may be obtained from BC Capital on 02380 221222

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