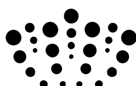 INTELLECTUAL PROPERTY OFFICE

BL O/405/10

25 November 2010

PATENTS ACT 1977

APPLICANT	Microphage Incorporated
ISSUE	Whether patent application GB 0813683.0 complies with section 1(1)(b)
HEARING OFFICER	Dr L Cullen

Introduction

1. International patent application PCT/US2007/002275 entitled "Method and apparatus for determining level of microorganisms using bacteriophage" was filed on 26 January 2007 in the name of Microphage Incorporated and claimed priority from three earlier applications; US 60/762,749 filed on 27 January 2006, US 60/794,652 filed on April 2006 and US 60/800,922 filed on 15 May 2006. The international application was published by WIPO as WO 2007/087439 on 02 August 2007, entered the UK national phase as GB 0813683.0 and was re-published as GB 2447826 on 24 September 2008.

2. The first examination report dated 15 August 2008 was an abbreviated report adopting the International Preliminary Report on Patentability that was issued on 29 July 2008 in which two prior art documents were cited in support of novelty and inventive step objections. On 13 February 2009 the applicant submitted arguments in relation to the cited prior art documents. Following a top-up search, the examiner cited three further documents and maintained the inventive step objections in his examination report dated 20 May 2009. In three additional rounds of correspondence between the applicant and the examiner, the applicant was unable to persuade the examiner that claims relate to an invention that meets the requirement for an inventive step.

3. The matter came before me at a hearing on 03 August 2010. The applicant was represented by Dr Andrew P. Hartley, a patent attorney from Mathisen, Macara & Co. The examiner, Dr. Jeremy Kaye, also attended.

4. An official letter dated 21 July 2010 was issued by the examiner to summarise the issues to be considered at the hearing. In response to this, and in advance of the hearing, in a letter dated 28 July 2010, the applicant's attorney filed an alternative set of claims to replace those on file and which were to form the basis of discussions at the hearing.

The application

5. The application concerns a method to quantify the amount of a harmful bacterium in samples taken from humans. If the amount of this bacterium is above a threshold level, remedial action is required. The application indicates that merely identifying the presence of the harmful bacterium in the sample is not sufficient to indicate if remedial action is required as such bacteria may normally be present in low concentrations in healthy humans.

6. The method for determining the concentration of a target bacterium in a sample comprises adding a known amount of a bacteriophage (or "phage") to the sample and, after a predetermined time, assessing the amount of a marker comprising, or associated with, progeny phage and making an assessment of the concentration of target bacterium using the level of this marker.

7. A bacteriophage, also referred to as phage, is a virus that infects bacteria. They attach to and inject genetic material into the host bacteria which are then induced to replicate the bacteriophage (amplification), producing phage progeny. Lytic bacteriophage rupture the host bacterium thereby releasing the progeny phage into the local environment to infect further bacteria. The time taken to infect, multiply and release progeny phage can take as little as one hour depending on the phage, host and conditions.

8. The applicant has discovered that if a prescribed amount of parent bacteriophage specific to a bacterium is added to a sample that includes the target bacterium, the time taken to develop an amplified level of progeny phage (or a biological marker associated with the progeny phage) can be correlated with the initial quantity of target bacteria in the sample. For a given amount of parent phage added to a sample, the time it takes to develop a characteristic phage (or related marker) level depends on the initial bacterial concentration in the sample. Thus, the concentration of bacteria that was present initially can be deduced from the concentration of phage measured at a specific time. As a result, it is possible to determine whether the bacterial concentration in an unknown sample is above or below a threshold concentration or the initial quantity of bacteria present.

The claims

9. The latest set of claims, which were filed with the applicants letter dated 28 July 2010 for consideration at the hearing, comprises four independent claims: 1, 5, 10 and 13.

10. Claim 1 relates to a method for determining if an initial concentration of a target bacterium is present in a sample in which the initial concentration is not known and reads:

    A method of determining if an initial concentration of a target bacterium is present in a sample in which said initial concentration is not known, said

method comprising:

(a) combining with said sample a known amount of parent bacteriophage having a concentration of less than 10^8 per milliliter, said bacteriophage capable of infecting said target bacterium to create a bacteriophage-exposed sample; and

(b) providing incubation conditions to said bacteriophage-exposed sample sufficient to allow said parent bacteriophage to infect said target microorganism and to multiply in said target microorganism to create in said bacteriophage-exposed sample a detectable marker comprising progeny bacteriophage or a biological substance associated with said progeny bacteriophage;

said method further comprising:

(c) waiting a predetermined time period correlated to said known amount of said parent bacteriophage such that, if said target bacterium is present in said sample at or above said initial concentration, said marker will be amplified in said sample to a specific marker level;

(d) assaying said exposed sample to determine the level of said marker; and

(e) determining whether said initial concentration of said target bacterium was present in said sample using the level of said marker.

11. Claim 5 relates to a method of determining the initial quantity of a bacterium in a sample and reads:

A method of determining the initial quantity of a bacterium present in a sample in which said initial quantity is not known, said method comprising:

(a) combining with said sample a known amount of parent bacteriophage having a concentration of less than 10^8 per milliliter, said bacteriophage capable of infecting said target microorganism to create a bacteriophage-exposed sample;

(b) providing incubation conditions to said bacteriophage-exposed sample sufficient to allow said parent bacteriophage to infect said target bacterium and to multiply in said target bacterium to create a detectable amplified marker comprising progeny bacteriophage or a biological substance associated with said progeny bacteriophage in said bacteriophage-exposed sample; and

(c) assaying said marker in said exposed sample to determine a marker level in said sample;

said method further comprising:

(d) measuring the reaction time to reach said marker level; and

(e) determining said initial quantity of said microorganism present in said sample using said known amount of bacteriophage, said marker level and said measured reaction time.

12. Claims 10 and 13 relate to methods of determining the susceptibility or resistance of a target bacterium to an antibiotic and comprise the methods of claims 1 and 5 respectively with the added step that the target bacterium are combined with an antibiotic prior to combining with the known amount of parent bacteriophage in step (a).

13. At the hearing, and also in a letter dated 12 August 2010, the applicant suggested an amendment to the independent claims of a further requirement that the measurement of phage progeny level is made when the bacteriophage is within its exponential growth phase. This would add the following requirement to claim 1 (see above for rest of claim):

    "… and wherein waiting a predetermined period comprises waiting until a time at which the bacteriophage concentration is increasing exponentially"

    and to claim 5 (see above for rest of claim):

    "… and wherein at said reaction time the bacteriophage concentration is increasing exponentially"

The Law

14. The examiner has raised an objection under section 1(1)(b) of the Patents Act 1977 that the invention does not involve an inventive step. The relevant parts of section 1 read as follows:

    1(1). A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say:

    (a) …;

    (b) It involves an inventive step;

    (c) …;

    (d) ….

15. Section 3 of the Act, entitled 'Inventive Step' reads:

    3. An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of Section 2(2) above (and disregarding Section 2(3) above).

16. The approach to assessing inventive step is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 ("Windsurfing") as modified by Jacobs LJ in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588 ("Pozzoli"). The modified approach, which Dr Hartley accepted was the appropriate one to follow, involves the following steps:

   (1)(a) Identify the notional "person skilled in the art";

   (b) Identify the relevant common general knowledge of that person;

   (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

   (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

   (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

Analysis

17. The following terms are used in the discussion below and are included here for ease of reference:
[ ] are used to indicate concentration, [P] = concentration of phage; [B] = concentration of bacteria; [P_0] = initial concentration of phage, i.e. concentration at time, t = 0; [B_0] = initial concentration of bacteria, i.e. concentration at time, t = 0

18. I will consider each step of the *Windsurfing/ Pozzoli* approach in turn:

1(a): Identify the notional "person skilled in the art".

19. The examiner identified the person skilled in the art as a team of microbiologists comprising bacteriologists and virologists with knowledge of the interaction between bacteria and bacteriophage. Dr Hartley accepted that such a team would represent the skilled person.

1(b): Identify the relevant common general knowledge of that person.

20. The examiner asserted that this skilled team would have knowledge of the interaction between bacteriophage and its target bacteria including an understanding of the kinetics of this interaction. The team would know how to monitor and record the interaction between bacteriophage and its target bacteria where the parent bacteriophage infects the target bacteria resulting in amplification of the bacteriophage to produce progeny bacteriophage. This team would also be aware of the various methods used to detect bacteriophage and their progeny. This knowledge would include how bacteria and bacteriophage grow in the presence of each other, how the parent bacteriophage takes over the

bacteria forcing it to produce bacteriophage progeny and ultimately how this leads to the death of the bacteria and the release of the progeny bacteriophage which can then go on to repeat the process. The examiner considered that the use of calibration curves for the quantitative determination of the concentration of one biological molecule, such as an enzyme or its substrate, or in this case, of bacteria or bacteriophage was also part of the common general knowledge.

21. The applicant did not agree with this assessment of the common general knowledge. While he considered that the skilled team would be aware of the interaction between bacteriophage and bacteria and that this can be used to determine the presence of absence of progeny bacteriophage, he did not consider that the skilled team would have sufficient knowledge of the kinetics of the interaction between bacteria and bacteriophage to be able to determine quantitatively the amount of bacteria that produces a particular amount of bacteriophage (or related marker of bacteriophage). He considered that the skilled person would be aware only that the kinetics between phage and bacteriophage was complicated. As a result, the applicant does not consider that use of calibration curves for the quantitative determination of the concentration of bacteria or bacteriophage was also part of the common general knowledge.

22. In support of his argument that the kinetics of the bacteriophage-bacteria interaction is known and is part of the common general knowledge, the examiner has cited the document referred to as KRUEGER[1] [i.e., *J. Gen. Physiol*. Vol.14, 1930, Krueger, A.P. & Northrop, J. H., "*The kinetics of the bacterium-bacteriophage reaction*", pp.223-254]. Dr Hartley did not think that the subject matter contained within this document formed part of the common general knowledge, but, he was of the view, that considering it as such would not be an issue.

23. I consider that KRUEGER is, despite Dr Hartley's assertion to the contrary, part of the common general knowledge. I am satisfied that all the information in this document in relation to the kinetics of the bacterium-bacteriophage interaction would have been available to the skilled team before the priority date. The interaction between phage and bacteria has been known for a long time so I do not consider that the age of the KRUEGER document which was published in 1930 is a significant factor. Work on bacteriophage was conducted in the early part of the 20th century to explore the potential use of bacteriophage as possible agents to treat bacterial infections in humans. While this work was larger overtaken by the discovery of antibiotics, bacteriophage remained an important field of study in relation to the structure of DNA and how viruses infect cells. Thus I consider that a skilled team that comprises bacteriologists and virologists, as in the present case, will have a good knowledge of the interaction between bacteria and bacteriophage. I consider that they will be aware of work such as that described in KRUEGER which describes the kinetics of the interaction between bacteriophage and bacteria.

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[1] The KREUGER document is available online via the US National Centre for Biotechnology Information (NCBI) (see website at http://www.ncbi.nlm.nih.gov/ for further details); the full text of the article is available at http://www.ncbi.nlm.nih.gov/pmc/articles/pmc2141107/pdf/223.pdf .

2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it.

24. The inventive concept identified by the examiner is a method for determining the initial concentration of a target bacterium in a sample by measurement of a marker of progeny bacteriophage, or a substance associated with progeny bacteriophage, following incubation of the bacteria with a known amount of parent bacteriophage over a particular time period.

25. The inventive concept identified by the applicant is a method of determining whether a bacterial concentration in a sample is at, or greater than, a certain pre-determined amount and involves incubating the sample with the pre-determined amount of phage for a pre-determined time and then, after that time, either measuring the level of the phage or some biological marker associated with the phage. Depending on the level of that measurement, it is possible to determine whether the initial level of bacteria in the sample was at, or above, a pre-determined level or not.

26. Dr Hartley was of the opinion that the examiner's assessment of the inventive concept was correct with respect to claim 5, where an initial quantity was being determined, but was not correct with respect to claim 1 which, he argued was less limiting, in that it doesn't require one to know what is the actual initial level of bacteria but only whether the initial level is above or below a known threshold.

27. I do not consider the differences between these two positions is significant. Both methods rely on determining the initial concentration of bacteria in a sample following incubation with a known amount of phage over a known period of time; whether the resulting outcome is provided as a numerical quantity or as an indication of being above or below a pre-determined figure does not matter in my view. It is my view that if it is a condition that the level of the bacterium in the sample to be determined is at, or above, a pre-determined figure, than a determination of the actual quantity in this sample would be an inherent part of that procedure. Indeed, in the present application at page 7, lines 29-32 it is stated that: "In this disclosure, determining the quantity of a microorganism is equivalent to determining the concentration of the microorganism, since if you have one you have the other…"

28. Thus I consider that the inventive concept of the present application is a method for determining the concentration of a target bacterium in a sample by measurement of a marker of progeny bacteriophage, or a substance associated with progeny bacteriophage, following incubation of the bacteria with a known amount of parent bacteriophage over a particular time period.

3. Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

29. The examiner has cited four documents; US 2005/0250096 (WHEELER), WO 2003/035889 (INVESTIGEN), WO 2005/001475 (VOORHEES) and WO 2003/087772 (COLORADO) in addition to KRUEGER citation already mentioned

as indicating the state of the art.

30. KRUEGER describes in some detail the interaction between a bacterium, *Staphylococcus aureus*, and bacteriophage that is highly active and specific for this bacterium, referred to as antistaphylococcus bacteriophage. The experimental results and analysis of the kinetics of this bacterium-bacteriophage reaction show that such a reaction is suitable for quantitative analysis of the bacterium-bacteriophage system. WHEELER, INVESTIGEN, VOORHEES and COLORADO all describe methods that use bacteriophage in the detection of bacterial species based on the process of bacteriophage amplification and detection of progeny bacteriophage.

31. Both examiner and applicant considered that KRUEGER was the most relevant of the citations in terms of defining the quantitative aspects of the bacteriophage-bacteria interaction. I agree.

32. Dr Hartley explained that the main differences between claim 1 and the cited art is that of determining whether the initial concentration of bacteria was above or below a known threshold value. He explained that "known" was something that you can quantify in numbers and that this threshold is identified by some means prior to performing the method of claim 1. At page 10, lines 27-29, of the application, it states:

    "*Preferably, prior to the test, a table of time to the detection point versus microorganism concentration is made based on a range of measured results. If a time is between points on the table, then extrapolation may be used to determine the initial concentration"*

    This indicates in my view that the preparation of a calibration curve to relate time to detection point (or progeny phage) versus initial bacteria concentration is regarded by the applicant as a standard or well known procedure

33. This method of claim 1 will give a positive result, i.e. a detectable level of bacteriophage only if the initial concentration of the bacteria is at or above this threshold value, if it is below this value it will not lead to the production of sufficient bacteriophage to be detected. Dr Hartley indicated that the level of $[P_0]$ is less than 10^8 per mL (i.e. $\log [P_0] < 8$) as this makes the amplification and progeny phage detection assay more effective. The level is set below the detection limit of phage using the various techniques referred to in the application and so only when amplification has taken place will sufficient phage be produced to give a detectable result. For claim 5, the main difference to claim 1, is that one is determining the actual, initial concentration of bacteria.

34. At the hearing, Dr Hartley began by stating that KRUEGER is an academic study concerning the kinetics of the bacteriophage-bacteria interaction and that the disclosure therein and Figures 2-5, referred to by the examiner, do not actually allow the determination of the initial concentration of bacteria or whether a threshold level is exceeded: all they show is the kinetics of a reaction under certain conditions where the bacteria concentration is kept constant and the parent phage concentration is varied. He does not consider that it would be

possible to work backwards and find the initial level of bacteria from a measured value of progeny phase bacteria taken at a specific time after addition of a known value of parent phage. He explained that the reason for this was that nowhere in KRUEGER is there a series of experiments in which the level of phage is kept constant and the level of bacteria varied. The opposite, as shown in Figure 11 of KRUEGER, was carried out, wherein the level of bacteria is kept constant and the level of initial phage concentration is varied.

35. Dr Hartley continued by comparing Figures 4 and 5 of KRUEGER and suggested that it is not possible to determine from these two graphs why it takes longer to reach a log [total P] of 10: ~3h in Figure 5 versus ~1.7h in Figure 4. He asked whether this is because [P_0] is lower in Figure 5 or because [B_0] is lower than in Figure 4. He also stressed that none of the graphs in KRUEGER show different initial bacterial concentrations and the same initial phage concentration.

36. Dr Hartley then asserted that, in comparison to chemical reactions or biological reactions such as those involving enzymes and their substrates, where the kinetics are well understood and calibration curves would be commonly used as a means to obtain quantitative data, the skilled person would know that the interaction between phage and bacteria is more complex and that the kinetics do not lend themselves to that type of analysis, *i.e.* preparing calibration curves would not be considered an obvious thing to do. Dr Hartley submitted that KRUEGER puts forward a series of experiments that describes some of the kinetics of the phage-bacteria interaction but it does not represent the whole of the relationship. He argued that it is not possible to determine from Figures 2-5, or from the disclosure in KRUEGER in general, if there is a linear, proportionate relationship without creating a calibration curve. Given the conclusions made in KRUEGER, it's not possible to tell, when you increase the initial bacterial levels in Figure 5, for example, whether the progeny phage level would go up or down. Dr Hartley did accept that there was a relationship between progeny phage level and initial bacterial concentration but considered that it was not fully known from KRUEGER.

37. Dr Hartley then discussed some of the conclusions drawn from the KRUEGER document, namely points (b), (d), (f) and (j) at pages 251-252, and explained how these points demonstrate the complexity of the relationship between phage and bacteria and how this would lead the skilled person away from considering the use of curves such as those in Figures 2-5 to determine bacterial concentrations by creating calibration curves for example. Briefly, these conclusions state that bacterial growth is essential for phage formation, that during logarithmic bacterial growth phage formation is also logarithmic but proceeds at a faster rate, that lysis begins when log $[P] / [B] = 2.1$ and that during lysis of the bacteria a considerable percentage of phage are destroyed.

38. Dr Hartley then referred to the remaining cited prior art and, although accepting that all disclosed methods of detecting bacteriophage as a means to detect bacteria, stressed that each of them was concerned with detecting the presence or absence of a bacteria and not quantification. I accept that the WHEELER, INVESTIGEN, VOORHEES and COLORADO documents do not disclose how to quantify the bacteria that is detected using the methods described in these

documents.

39. Turning to the analysis presented by the examiner in his various examination reports and re-affirmed at the hearing, he has referred to Figures 2-5 at page 225 of KRUEGER which show graphical plots of typical kinetic experiments showing the curves of log [total phage, P] per ml against time and log [total bacteria, B] per ml against time for different initial values of phage [P_0] and bacteria [B_0] at a constant temperature. These figures are reproduced in the Annex to this decision. The examiner has argued that these figures show very similar curves to those given in Figure 1A of the present application which is also reproduced in the Annex to this decision. This figure illustrates how bacteriophage amplifications, described in detail at pages 8-9 of the specification, can be used to determine the quantity of a microorganism. It depicts the growth kinetics of a bacterium-bacteriophage interaction and provides a graph (10) of phage concentration versus time for a test sample initially containing 10^4 target bacteria, and also a graph (20) showing the concentration of target bacteria versus time for the same test sample with 10^4 phage added at time zero. The third paragraph on page 8 of the specification goes on to describe what happens in this situation as bacteria and phage numbers increase. This leads, in the case of the bacteria, to a steep decrease in bacteria numbers as the phage infect and kill them and, in the case of the phage, to a leveling off in its growth as the majority of the bacteria are killed. At page 9 of the application it is explained that the inventors have determined that graph (10), for example, is not just qualitative, it can be used quantitatively *i.e.* it is possible to relate the level of phage to an initial concentration of target bacteria.

40. The examiner argues that such a relationship, *i.e.* the correlation between the level of phage at a particular time point to initial starting bacterial concentration, is made from the curves given in Figures 2-5 of KRUEGER: at any time point the progeny phage concentration can be related to the input of target bacteria. For example, from Figure 5, at Time, T = 3 hours, the value of log [total phage P] of ~10 is related to an input concentration of bacteria [B_0] of ~7.5 with a [P_0] of ~4,5, whilst in Figure 4, a log [total phage P] of ~10 is reached at ~1.75 hrs and relates to [B_0] of ~8.5 when [P_0] of ~7.

41. It is the examiners view that these graphs clearly indicate that there is a relationship between input bacteria concentration and levels of progeny phage produced at particular time points given a known input of parent phage concentration. Figure 3 for example shows what happens to the progeny phage level over time when log [B_0] is ~7.4 and [P_0] is ~4.8. Such a graph indicates that at a specific time, a certain concentration of progeny phase will be produced from an initial bacteria concentration of ~1 x $10^{7.4}$ i.e. log [B_0] = ~7.4, by a concentration of parent phage of ~1 x $10^{4.8}$ i.e. log [P_0] is ~4.8. If a sample was measured at time = 2 hours (120 minutes) after addition of a parent phage concentration of log [P_0] = ~4.8 and found to contain progeny phage (or related marker) concentration of log [P] = ~9.2, then this curve would tell you that the starting concentration of bacteria would be log [B_0] = ~7.4. Similarly, from Figure 4, if you added a parent phage concentration of log [P_0] = ~7 to a sample of bacteria and obtained a progeny phage concentration of log [P] = ~9.4 after 2 hours you know that this has been produced from an initial bacterial

concentration log [B_0] = ~8.2. Similarly, from Figure 5, if you added a parent phage concentration of log [P_0] = ~4.4 to a sample of bacteria and obtained a progeny phage concentration of log [P] = ~8.1 after 2 hours you know that this had been produced from an initial bacterial concentration log [B_0] = ~7.4.

42. The examiner contends that such a relationship as shown in Figures 2-4 could be extended to assessing unknown concentrations of bacteria using the common general knowledge of the skilled person who would know about standard laboratory investigations of microorganisms such as bacteria and viruses including the preparation and use of calibration curves to obtain quantitative data. Thus, if one determines a phage concentration in a sample, using a calibration curve, one can work out the initial concentration of bacteria that would have produced that amount of phage at a specific time.

43. The examiner has asserted that the difference between what is provided in the KRUEGER document and the inventive concept is the manner in which the progeny bacteriophage are detected. However, the remaining cited prior art (WHEELER, INVESTIGEN, VOORHEES and COLORADO) provide methods for detecting bacteria in a sample by detecting progeny phage following infection, amplification and lyses. I do not need to explain in detail these documents just to confirm that that they do indeed provide methods for such detection. I will note however that COLORADO refers to use of initial amount of bacteriophage (or its associated marker) that are below the detection limit of bacteriophage (or its associated marker).

4. Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

44. It seems to me that the crucial decision to be made here is whether KRUEGER provides sufficient disclosure for the skilled person to arrive at a method for determining a concentration or quantity of bacteria in a sample using a known input of phage, without the need for any inventive ingenuity. I consider that methods of detection of progeny phage are well known.

45. The discussion of the bacterium-bacteriophage interaction in KRUEGER indicates that the reaction between bacteriophage and bacterium can only take place when the bacterium is growing and that the growth of the bacteriophage takes place at a much faster rate than the growth of the bacteria, i.e. the rate of production of phage is proportional to a power of the rate of production of the bacterium until a specific [P] is reached per [B], i.e. [P] / [B] = 125 or log [P] / [B] = 2.1. The conclusion drawn is that the behaviour of phage (see for example, page 241 and (e) on page 252) is:

> "*suggestive of the manner in which a relatively simple chemical compound would be distributed and is not at all typical of the distribution one would expect if bacteriophage is a comparatively complex substance*"

46. In KRUEGER, [B_0] is known, and [P_0] is known and the level of [P] at any particular time point can be related to this starting concentration. It explores what

happens to [P] when [B_0] is kept constant and [P_0] is varied. This allows one to produce a calibration curve that allows the quantitative determination of the initial concentration of parent phage required to ensure the bacteria reaches a specific final concentration, see for example, Figure 17 and discussion on the kinetics of bacteriophage action (pages 243-249).

47. I do not think it unreasonable to assume that the person skilled in the art, when confronted with the disclosure in KRUEGER, would consider creating a calibration curve to enable the determination of unknown bacteria in a sample using amplification of bacteriophage. I am convinced that the skilled person would have assessed there to be a reasonable expectation of success in doing such experiments and would arrive at a method that would allow the detection of unknown initial starting concentrations of bacteria [B_0]. Such experiments are considered commonplace, for example, when investigating kinetics of chemical reactions or reactions of enzymes with substrates and this has been accepted by the applicant. The skilled person would not, in my opinion, require any inventive ingenuity in coming up with such calibration curves: they would be part of his common general knowledge. I can find nothing in KRUEGER pointing away from doing this and, even though Dr Hartley contends this would not happen I do not agree: there would be a likelihood of success and determination of unknown concentrations of bacteria in a sample would be nothing more than routine experimentation, requiring no inventive ingenuity on behalf of the skilled person.

48. In the application in suit, the applicant explores what happens to [P] when [P_0] is kept constant and [B_0] is varied. This allows one to produce a calibration curve that allows the quantitative determination of the initial concentration of bacteria required to ensure that progeny phage reaches a specific final concentration. I consider that what the applicants are doing is no more than has been accomplished in KRUEGER and represented in Figures 2-5: they have created a curve using a known amount of input bacteria [B_0] and input phage [P_0] and have noted the kinetics, i.e. the rate of increase in the progeny phage concentration and the rate of growth and then decline of the bacteria concentration. This is described at page 9, and depicted in Figure 1A which shows the relationship that exists between the level of phage progeny at a pre-determined time T_p and [B_0] such that phage progeny levels may be used to determine either a specific quantity of [B_0] or whether [B_0] is at or above a certain level. Figure 2A in the application in suite shows the same data as Figure 1A except in this example [B_0] is higher (log [B_0] = 6). The same amount of phage (log [P_0] = 4) is added in both samples (see Figures 1A and 2A). Considering these graphs together shows the effect of increasing [B_0] while adding the same amount of parent phage on the time it takes to detect progeny phage. It is necessary in my view to combine the results from Figures 1A and 2A in order to produce a calibration curve that would allow one to determine quantitatively the amount of initial bacteria required to produce a measured value of progeny phage at a specific time after the parent phage was added to this initial concentration of bacteria. The applicants have not mentioned any complex kinetics that they would need to consider in reaching their conclusion but state there is a relationship that may be used to determine [B_0], something that I believe the skilled person would realise given KRUEGER.

49. The differences between Figures 4 and 5 of KRUEGER pointed out by Dr

Hartley, and the uncertainty in determining why it might take longer to reach a particular phage progeny concentration given different starting concentrations of bacteria and/or parent phage does not, in my opinion, alter this conclusion. The skilled person to my mind would be aware that by considering one of these graphs, for example, Figure 5 and, keeping [P_0] at the same level (~4.4), it would be possible to vary [B_0] to obtain a series of values for a calibration curve. There would be no need to compare the two Figures 4 and 5 to come up with the experimental methodology necessary to produce a method to determine an unknown concentration of bacteria.

50. Contrary to what Dr Hartley contends, I do not believe that the skilled person would not consider the construction of calibration curves for the quantitative determination of [B] given the disclosure in KRUEGER. I can find nothing in KRUEGER that would lead the skilled person away from investigating the bacteria/phage interaction and creating calibration curves in a manner that Dr Hartley maintains they would not. Given that there is a predictable relationship between [B] and [P] when [P] is varied that is amenable to quantification using calibration curves, it would not be inventive to consider the relationship between [B] and [P] when [B] is varied and so use calibration curves to allow determination of the initial level of bacteria as proposed in the present application.

51. The fact that Dr Hartley suggests a complicated interaction is described in KRUEGER does not, in my view, negate the fact that there is a relationship between input bacteria concentration and phage progeny level. I therefore do not believe that this complexity of the interaction precludes the production of a calibration curve of the kinetics. All that is required is that there is a consistent relationship between the bacteria and bacteriophage that can be measured and plotted.

52. Figure 11 in KRUEGER shows an experiment wherein the bacterial concentration is kept the same and [P_0] is varied. In relation to this experiment and also those shown in Figures 2-5, Dr Hartley pointed out that in reactions where [P_0] is low compared to [*B*], a longer time will be required to lyse than those having an original log [P] / [B] closer to 2.1 and that there will be lack of growth or very slight growth seen in cultures to which have been added very high [*P*]'s. He sees these as concerns that would lead the skilled person away from using the teaching of KRUEGER to construct calibration curves as a means to determine unknown bacterial concentrations [B_0]. However, although these conclusions are indeed correct, since these features are noted in this paper they are not unknown to the skilled person and may be considered during further experimentation. KRUEGER explains, at page 237, in the section entitled "*H. Lytic Destruction of B Is a Logarithmic Process*" in relation to what is occurring in Figure 11, that:

> "*…B destruction is logarithmic with time, in this respect being analogous to most death rate processes. Further the rate at which lysis proceeds with an initial bacterial concentration is constant for widely varied P_0's*."

53. This suggests that over a wide range of [P_0] values the kinetics reaction gives constant, and presumably uncomplicated, results. It is not suggested that such experiments would prove exceptionally difficult or provide spurious or inaccurate

results. Consequently the skilled person would not be put off from undertaking experiments wherein the [P] is kept constant and the [B] is varied.

54. Hence I do not consider the invention as claimed in claims 1 and 5 involve an inventive step over KRUEGER when combined with the common general knowledge.

Conclusion

55. I conclude that the invention as defined in independent claims 1 and 5 is lacking an inventive step. Claims 10 and 13 relate to the testing of the susceptibility or resistance of a bacterium to an antibiotic by first combining the test bacterium with the antibiotic and then carrying out the method of either claim 1 or claim 5. Addition of this susceptibility/resistance determination to the methods of claim 1 or 5 does not provide an inventive step given the common general knowledge. Regarding the appendant claims, I am of the view that the features disclosed therein would be common in this technical field and would not confer inventiveness on their respective independent claims.

56. I would also consider that amendment to the claims along the lines suggested at the hearing, relating to taking measurements in the exponential growth phase of the bacteriophage, is also not considered inventive since this would be considered to be the norm in such kinetics assessment, i.e., making measurements during the exponential growth phase of a microorganism, such as bacteriophage, would be expected to yield the most reproducible results. Thus I do not consider that this would provide the claims with an inventive step.

57. I note that in a letter dated 12 August 2010 the applicant would like further opportunity to amend the claims in the eventuality that I found that the claims currently on file lack an inventive step but as I have indicated above I do not consider the present application is inventive.

58. The extended period for putting the application in order expired on 27 September 2010. As the application was not in order on that date, the application is refused under Section 18(3) as failing to meet the requirements of inventive step under Section 1(1)(b) of the Patents Act 1977.

Appeal

40 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

Dr L Cullen
Deputy Director acting for the Comptroller

ANNEX – Patent Application GB0813683.0, Microphage Inc.

Figure 1A and **Figures 2-5** as referred to in the text of the decision.
Figure 1A is reproduced from the patent application as published by WIPO as WO 2007/087439. Please refer to published specification for further details.
Figures 2-5 are reproduced from J. Gen. Physiol., Vol.14, 1930, Krueger, A. P. & Northrop, J. H., "*The kinetics of the bacterium-bacteriophage reaction*", pp.223-254 which is available on-line at http://www.ncbi.nlm.nih.gov/pmc/articles/pmc2141107/pdf/223.pdf. Please refer to the full article for further details.

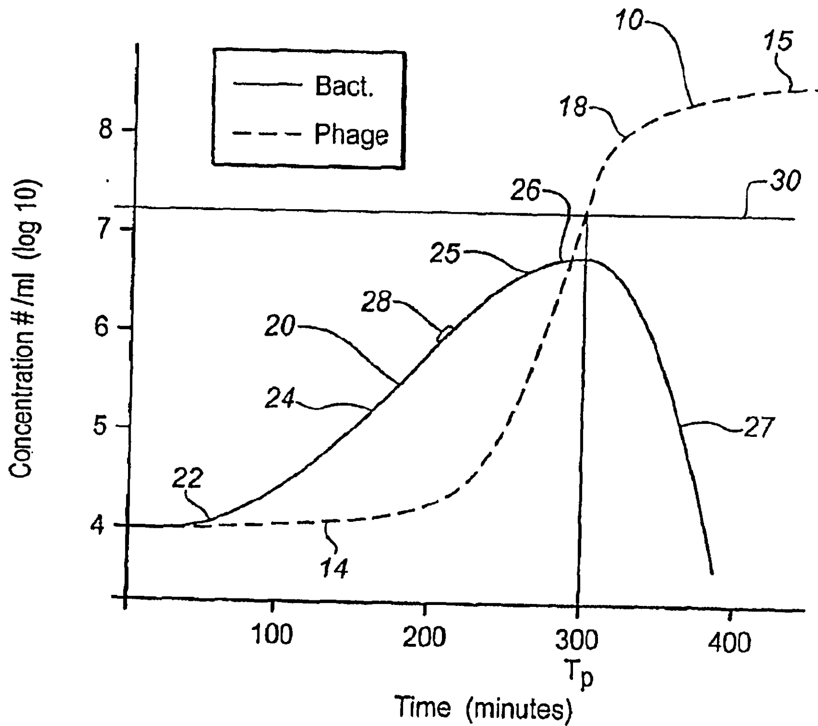

FIG. 1A

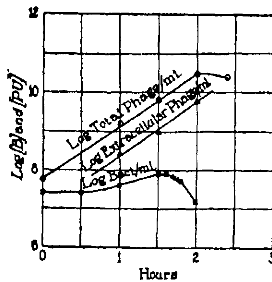

FIG. 2

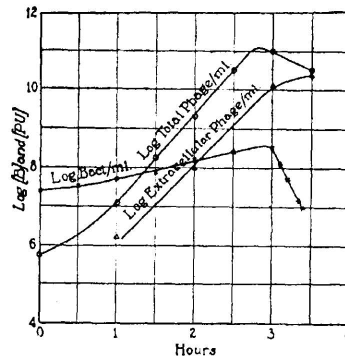

FIG. 3

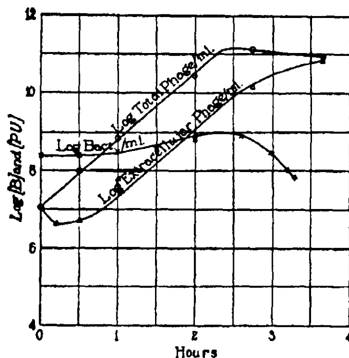

FIG. 4

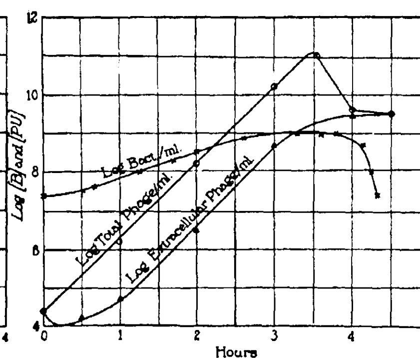

FIG. 5

FIGS. 2, 3, 4 and 5. Plots of typical kinetic experiments. The curves of log total [P], log extracellular [P] and log [B] against *t* for different values of *Po* and *Bo* at 36°C. are shown.