THE JOINT EXAMINATION BOARD

PAPER P6

INFRINGEMENT AND VALIDITY OF UNITED KINGDOM PATENTS

22nd April 1994

10.00 am - 2.00 pm

Please read the following instructions carefully. This is a ***FOUR HOUR*** Paper.

1. Write on one side of the paper only using ***BLACK*** ink. You must write your examination number and the designation of the Paper in the top right hand corner of the sheet. You must not state your name anywhere in the answers.

2. No printed matter or other written material may be taken into the examination room.

3. Answers ***MUST*** be legible. If the examiners cannot read a candidate's answer no marks will be awarded.

ADVISE TO CANDIDATES

1. Although the subject matter of the question this year is different, exactly the same principles of interpretation apply when assessing infringement and validity.

2. Read the question and documents supplied carefully ***as they contain all the technical information you need to answer this question.***

3. The Examiners award marks more for the reasoning shown by candidates than for the conclusions reached.

4. You should in your answer consider any amendment that Company A, the proprietor of patent A, might make to its patent and the possible effect thereon on your client's position.

5. You should also consider what changes your client might be able to make to its product.

QUESTION

The date is 22nd April 1994 and you have just received the following letter from your client, Company C:-

"We recently received, and copy herewith, a letter from some Solicitors which said they were acting for Company A and that our sterilising compound C infringes their United Kingdom Patent A.

We are very surprised at this because we know about Company A's sterilising solution, which is sold in a concentrated form and which only requires dilution with distilled water in the usual method before use. Our product, compound C launched some two years ago, is sold in two-part form, part 1 being glutaraldehyde and part 2 containing a buffering agent - usually sodium borate, although we could use sodium phenate - part 2 also includes magnesium salts.

We give instructions with our composition for part 1 (the glutaraldehyde) to be diluted with distilled water to achieve an approximately two per cent solution (this is usual practice) and then for part 2 (the buffering agent and magnesium salts) to be added until, by testing with litmus paper provided, until the litmus paper turns pink showing the composition to be acidic. This is a rough and ready test which should produce a composition with a pH of between 6.0 and 7.0, which is necessary to lengthen the effective life of the prepared sterilising solution.

We also give instructions that the sterilising solution made up of parts 1 and 2 should be regularly tested, with further litmus paper we provide, with the warning that, once the litmus paper no longer turns pink, the sterilising solution has lost its efficiency and should be discarded.

We have just re-read this letter and notice that they are asking for a reply within 14 days, that is by today, 22nd April 1994.

What shall we do?

The copy letter from Company A's Solicitors that accompanies your client's, Company C, letter reads as follows:-

"8th April 1994

We act for Company A. Your sterilising compound C infringes our client's United Kingdom Patent No. A and, if you do not immediately stop sales and within 14 days from the date of this letter give your written assurance to reimburse our client for past sales at 20% royalty of your ex-works price, we will commence infringement proceedings against you in the High Court."

You immediately check the U.K. Register, find that Company A's United Kingdom patent is in force, being some 10 years old. No licences are shown to be recorded against Company A's patent.

You obtain a copy of the granted specification (B Series) and note that no citations are shown in the document. However, a search of the INPADOC Priority Database shows there to be a corresponding United States patent and, investigation of the United States patent shows there to be one citation, United States Patent No. B. A further search of the INPADOC Patents Family Database shows United States Patent B to have issued before the priority date of Patent A and there to be no foreign equivalents to this United States Patent B. You obtain a copy of United States Patent B from the library using their fax service.

Write notes upon which you will base your advice to your client.

PATENT A

STERILISING SOLUTIONS

This invention relates to improved chemical sterilising solutions, and is particularly related to sterilising compositions containing a dialdehyde as a sporicidal and bacterial agent.

United Kingdom Patent Specification Nos. X and Y disclose sterilising solutions comprising an n-alkane dicarboxyaldehyde and an alkalinating agent to ensure that the pH of the solution is above 7.4.

It is stated in these Patent Specifications that the composition has to be alkaline with a pH above 7.4 to obtain effective sterilising action. However, at alkaline pH, polymerisation of the dicarboxyaldehyde occurs, leading to a deterioration of the solutions and loss of sterilising activity.

The currently known commercial compositions are sold as two-part products, one part being a slightly acidic composition of glutaraldehyde and an alkanol; the other part being an alkalinating agent such as sodium bicarbonate. For use, these parts are mixed and diluted in water to give a 2% glutaraldehyde solution (on a weight to volume basis). This resulting solution has a limited working life, generally of 2-3 weeks, before polymerisation of the glutaraldehyde makes the solution ineffective.

According to the present invention, a sterilising solution comprises an n-alkane dicarboxyaldehyde in which the composition is acidic, with a pH less than 7.4, and includes

potentiating compounds to enhance the sterilising activity of the n-alkane dicarboxyaldehyde. The acidity of the composition enhances its shelf life and the potentiating compounds offset the loss in sterilising activity.

Advantageously, the acidity of the solution is buffered and the potentiating compounds comprise a non-ionic surfactant (which may be of the polyethoxyethanol group) and acts to facilitate penetration by the dicarboxyaldehyde.

An advantage of such sterilising compositions is that they can be produced as a one-part concentrate having a shelf life of the order of two years, and capable of dilution to a disinfecting concentration to give a solution having a working lifetime of up to 4 weeks. The working lifetime of the solution depends critically on both whether the water added is hard or soft, and on the nature of the container the solution is mixed and kept in. Since the primary cause of deterioration of the solution seems to be base-catalysed polymerisation of the dicarboxyaldehyde, a pH indicator may be used to show when deterioration has probably taken place.

The invention is illustrated by way of example in the following description. In the following all terms expressed as a percentage are on a weight per volume basis, i.e. grams of substance in a hundred millimetres of solution.

A suitable formulation comprises the following constituents:

Glutaraldehyde	2.0000%
Isopropanol	2.0000%
Magnesium Chloride .$6H_2O$	4.0600%
Surfactant Triton X-100 (Trade Mark)	2.0000%
Tetrasodium EDTA	0.2500%
Sodium Borate	0.0300%
Boric Acid	0.4000%
Phenol Red	0.0005%
Water	89.2595%
	100.0000%

The reasons for inclusion of these constituents are as follows:-

i) The glutaraldehyde is the main bactericidal agent, the isopropanol having bactericidal properties to augment the glutaraldehyde.

ii) The bactericidal activity of the glutaraldehyde is potentiated by magnesium ions, here provided in the form of magnesium chloride, which break down bacterial cell walls allowing ingress of glutaraldehyde. This process is augmented by the surface wetting effect of Triton X-100, a surfactant of the polyethoxyethanol group.

iii) pH controllers. The boric acid and sodium borate form a buffer at a pH of around 6.

iv) The tetrasodium EDTA prevents precipitation of calcium borate from the solution in the event of hard water being added to the solution.

v) The phenol red acts as an indicator to give a distinctive colour change in the range pH 6 to pH 8.5. Any other suitable indicator for the required pH range may be used e.g. litmus, bromothymol blue, naptholphthalein, cresol red, n-nitrophenol. Phenol red changes colour from yellow to carmine between pH 6.8 and 8.4. The solution would remain potent throughout the orange phase.

vi) The boric acid and sodium borate also act as corrosion inhibitors for metals, thereby allowing the sanitising solution to be used freely for surgical or dental instruments.

vii) Finally the Triton X-100 acts as a detergent, the EDTA enhancing the detergency.

The concentrations quoted above are for example only. In particular the glutaraldehyde concentration of 2% is given since this is the generally accepted level in the known sterilising formulations. Further dilution by 1:2 to 1:10 is possible to give disinfecting solutions, or even by 1:20 to give a weakly disinfecting solution for, e.g. sanitising work tops.

Although the above example only uses glutaraldehyde it will be clear that similar considerations apply to other dialdehydes such as succinaldehyde.

CLAIMS:

1. A sterilising solution comprising an n-alkane dicarboxyaldehyde in which the composition is acidic, with a pH less than 7.4, and includes potentiating compounds to enhance the sterilising activity of the n-alkaline dicarboxyaldehyde.

2. A solution as claimed in claim 1, wherein the n-alkane dicarboxyaldehyde is glutaraldehyde.

3. A solution as claimed in claim 1 or claim 2, wherein the pH is buffered to around 6.0.

4. A solution as claimed in any of claims 1 to 3, wherein the potentiating compounds comprise a non-ionic surfactant.

5. A solution as claimed in claim 4, wherein the potentiating compound is of the polyethoxyethanol group.

6. A solution as claimed in any preceding claim, wherein a pH indicator is included to show by a colour change when the pH of the composition has risen sufficiently to affect its shelf life and potency.

UNITED STATES PATENT SPECIFICATION B

This invention relates to aqueous chemical compositions for room temperature sterilisation with improved effectiveness and longer active life.

Efficient sterilisation methods are needed for medical, hospital, and industrial applications. For repeated use, medical and dental instruments and equipment require sterilising procedures which are safe, effective, and rapid. Yet, the existing procedures and methods are either cumbersome, time consuming, costly or lack merit.

Chemical sterilisation at room temperature has advantages over other means of sterilisation and, consequently, has received considerable attention over the years. Many "cold sterilising" compositions have been suggested to the art.

In order to satisfy the criteria for sterilisation, a chemical preparation must be capable of killing all forms of microbiological life, including spores which are highly resistant to sterilisation. Such a chemical preparation must be bactericidal, fungicidal, and virucidal as well as sporicidal. While disinfectants, germicides, and antiseptics are capable of destroying most disease causing organisms, usually they are not cidal to (pathogenic) spores and, therefore, are not chemo-sterilisers. Relatively few antimicrobial agents are truly sporicidal and usable as chemo-sterilisers.

In recent years, the most widely used aqueous chemical sterilising agent has been a buffered 2% glutaraldehyde solution. Glutaraldehyde solutions prepared with an acid pH are not ordinarily sporicidal at room temperature. However, when made alkaline, sporicidal activity in these solutions is very evident.

One of the problems encountered with alkaline glutaraldehyde solutions, however, is their lack of stability. Such solutions lose both their sporicidal activity and identifiable glutaraldehyde in about 2 weeks after they are made alkaline. Another problem with the alkaline 2% glutaraldehyde solution is the relatively long contact time (10 hours at room temperature) required for sterilisation. Thus, the commercially available alkaline glutaraldehyde compositions exhibit limited active life and require lengthy immersion time for sterilisation i.e., the suppliers advise against using the activated solution more than two weeks, and call for an immersion time of at least 10 hours at room temperature. Acid glutaraldehyde compositions are claimed to be relatively more stable than alkaline glutaraldehyde and have extended use life, but the acid glutaraldehyde compositions are not sporicidal at room temperature.

The composition of the present invention exhibits improvements in stability and active life, with the activated solution having a sterilising use life of more than 30 days and sterilising properties within 6 ½ hours, at room temperature.

The present invention is an aqueous composition containing glutaraldehyde, 0.75-4.0% by weight, together with phenol and a metallic salt of phenol in total from 4-15%. The composition may also include, optionally, additional buffering agents, preferably 1-5% sodium borate, anionic and/or non-ionic surfactants in total from 2-10% and a humectant such as glycerol, propylene glycol or diethylene glycol from 2-10%.

Glutaraldehyde is acidic and, by itself, does not sterilise (i.e. is not sporicidal) at room temperatures. United States Patent Specification No. 1,234,567 discloses that by adding an appropriate alkaline buffer to

glutaraldehyde, the resultant solution becomes an active sporicide in the pH range of 7.4 to 10.0. However, in alkaline solution glutaraldehyde tends to polymerise and lose its sporicidal activity. Also, alkaline glutaraldehyde is not pH stable. Consequently, the alkaline glutaraldehyde sporicidal formulations tend to lose effectiveness over a period of time. As mentioned above, the various alkaline glutaraldehyde compositions marketed offer instructions not to use the (activated) solution after 14 days. A substantial increase in the active life of a buffered glutaraldehyde would constitute an advance in the art.

An additional area wherein improvement is desired is in kill time, this being the immersion period required for complete sterilisation. Alkaline glutaraldehyde formulations with 2% glutaraldehyde as the only active ingredient are generally accepted to have a 10 hour sterilising time. Increasing the glutaraldehyde concentration may help, but 4% glutaraldehyde is not significantly superior to 2% glutaraldehyde as a sporicide.

The compositions of this invention are a combination of buffered phenol and glutaraldehyde. Separately, phenol, phenolic derivatives or glutaraldehyde are not capable of room temperature sterilisation. (Alkaline glutaraldehyde is, of course).

Also, it has been found that the combination of glutaraldehyde and buffered phenol substantially increases the active life of alkaline glutaraldehyde compositions. The buffered phenol/glutaraldehyde combination is effective at pH levels below 7.4 as well as in the more alkaline range above 7.4. However, a pH of below pH 7.4 is preferred because improvements in solution stability are apparent in this lower pH range.

The buffered phenol/glutaraldehyde combination,

particularly the preferred formulations, has an active sterilising life of more than 30 days, requires 6 ½ hours (and possibly less) immersion time to achieve complete sterilisation at room temperature. The buffered phenol composition, without glutaraldehyde therein, has a shelf-life of 5 years, or more.

The improvement in useful life and in kill time exhibited by the composition of the present invention is reflected by the improved stability. A more effective glutaraldehyde steriliser composition will take longer to decline to the minimally acceptable effectiveness levels. An improvement in stability provides the user with a composition which retains a higher percentage of its original (kill) activity over the rated use period for the composition.

The fact that effectiveness has been improved by presence of buffered phenol also is evidenced by pH scan studies showing that the sporicidal activity of composition is less limited by pH. Specifically, the composition is effective over the range of pH 7 to 10 and apparently is effective at room temperature at pH-7. In practice, the pH range of 7.0 to 7.4 is preferred, because improved stability is believed to be achieved in this range. The composition may be adjusted to the desired pH by addition of hydrochloric acid or reduction of a buffer, or both.

The presence of sodium tetraborate (sodium borate) has been found to be useful as a buffering agent in quantities of from 1 to 5% by weight.

Also, a phenate, preferably sodium phenate 0.5 to 5% by weight, is used as a buffering agent. The concentration of phenol/phenate is a 4 to 15% with the phenol range being 3 to 10% by weight. preferably the phenol to sodium phenate ratio is from 5:1 to 7:1.

Surfactants are desirable ingredients, serving to facilitate penetration of active ingredients into pores, crevasses and irregular surfaces of objects being sterilised by immersion into the aqueous formulation.

In practice, presence of anionic and/or non-ionic surfactants individually or in various combinations, have been found effective. A combination of surfactants with a ratio of 60:40 to 40:60 anionic and non-ionic is preferred. Exemplary surfactants are sodium n-dodecylbenzene sulfonate and sodium cocoyl sarcosinate. The surfactants improve activity of the formulation. Tests with varying levels of surfactant concentration indicate that a high surfactant content, i.e., 2 to 10%, improve sporicidal activity for the composition as a whole.

Another ingredient that has been found desirable is a humectant selected from the group consisting of glycerol, propylene glycol and di-ethylene glycol, in quantities of from 2 to 10% by weight.

The full formulation is provided in a two-container form, one container holding the glutaraldehyde, e.g. as 25% or 50% solution, and the other container holding the buffer system.

The test formulation contained the following ingredients:

I	Buffered Phenol		% by wt.
a)	Phenol		7.05
b)	Sodium phenate		1.20
c)	Sodium borate		2.35
d)	Diethylene glycol		6.30
e)	Na-n-dodecyl benzene sulfonate (80% active material)		7.00
f)	Na cocoyl sarcosinate (30% active material)		10.95
g)	Distilled H_2O		50+q.s.
h)	6M hydrochloric acid		qs
			92.00
II			
	25% Glutaraldehyde		8.00
			100.00

Procedure:

Add ingredients a-f to a tared container, then add a large portion of the distilled water and stir. (The solution may be heated to 45°C to facilitate solution). With stirring, add (6M) hydrochloric acid or sodium hydroxide until pH reaches whatever value is desired in the pH 7 to 10 range. The non-adjusted pH is about 9.5. Add sufficient additional distilled water to being to proper total mass. (If heating is not used to facilitate solution, addition of the hydrochloric acid will dissolve the solids as the pH nears 7.5).

The buffered phenol system and glutaraldehyde are maintained in separate containers until needed. For use, the respective solutions are admixed.

WHAT I CLAIM IS:

1. An aqueous sporicidal composition comprising from 0.75 to 4.0% by weight glutaraldehyde and from 4 to 15% by weight of buffering agent.

2. A composition as defined in claim 1 wherein the buffering agent is a mixture of phenol and a metal phenate.

3. A composition as defined in claim 1 which additionally comprises at least one anionic or non-ionic surfactant.

4. A composition as defined in claim 1 which has a pH in the range from 7 to 7.4.

5. A composition as defined in claim 1 which has an active sterilising life of at least 30 days.