9610966-S SP

VAPOR STERILIZATION USING INORGANIC HYDROGEN PEROXIDE COMPLEXES

Related Applications

This application is a continuation-in-part of U.S. patent application Serial No. 08/369,786, filed January 6, 1995, which is a continuation-in-part of Serial No. 08/234,738, filed April 28, 1994.

Background of the Invention

Field of the Invention

This invention relates to an apparatus and process for using hydrogen peroxide vapor to sterilize articles such as medical instruments, and more particularly to the use of an inorganic hydrogen peroxide complex for such a process.

Description of the Related Art

Medical instruments have traditionally been sterilized using either heat, such as is provided by steam, or a chemical, such as formaldehyde or ethylene oxide in the gas or vapor state. Each of these methods has drawbacks. Many medical devices, such as fiber optic devices, endoscopes, power tools, etc. are sensitive to heat, moisture, or both. Formaldehyde and ethylene oxide are both toxic gases that pose a potential hazard to healthcare workers. Problems with ethylene oxide are particularly severe, because its use requires long aeration times to remove the gas from articles that have been sterilized. This makes the sterilization cycle time undesirably long. In addition, both formaldehyde and ethylene oxide require the presence of a substantial amount of moisture in the system. Thus, devices to be sterilized must be humidified before the chemical is introduced or the chemical and moisture must be introduced simultaneously. Moisture plays a role in sterilization with a variety of other chemicals in the gas

REPLACED SHEETS SG
☑ Description : paged ...1.... to paged ..50.....
☑ Claim(s) : paged ..51.... to paged ..54.....
☑ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged ...55... to paged .....
DATE OF RECEIPT .....

This Sheet Has Been Replaced

2-38018

or vapor state, in addition to ethylene oxide and formaldehyde, as shown in Table 1.

Table 1

Chemical	Relative Humidity Requirements for Optimal Efficacy	Literature Reference
Ethylene oxide	25-50%	1
Propylene oxide	25-50%	1
Ozone	75-90%	2
Formaldehyde	>75%	1
Glutaraldehyde	80-90%	3
Chlorine dioxide	60-80%	4
Methyl bromide	40-70%	1
β-Propiolactone	>75%	1
Peracetic acid	40-80%	5

1. Bruch, C. W. Gaseous Sterilization, *Ann. Rev. Microbiology* 15:245-262 (1961).
2. Janssen, D. W. and Schneider, P.M. Overview of Ethylene Oxide Alternative Sterilization Technologies, *Zentralsterilisation* 1:16-32 (1993).
3. Bovallius, A. and Anas, P. Surface-Decontaminating Action of Glutaraldehyde in the Gas-Aerosol Phase. Applied and Environmental Microbiology, 129-134 (Aug. 1977).
4. Knapp, J. E. et al. Chlorine Dioxide As a Gaseous Sterilant, Medical Device & Diagnostic Industry, 48-51 (Sept. 1986).
5. Portner, D.M. and Hoffman, R.K. Sporicidal Effect of Peracetic Acid Vapor, *Applied Microbiology* 16:1782-1785 (1968).

Sterilization using hydrogen peroxide vapor has been shown to have some advantages over other chemical sterilization processes (see, e.g., U.S. Pat. Nos. 4,169,123 and 4,169,124), and the combination of hydrogen peroxide with a plasma provides additional advantages, as disclosed in U.S. Pat. 4,643,876. In these disclosures the hydrogen peroxide vapor is generated from an aqueous solution of hydrogen peroxide, which ensures that there is moisture present in the system. These disclosures, together with those summarized in Table 1, teach that moisture is required for hydrogen peroxide in the vapor phase to be effective or to exhibit its maximum sporicidal activity. However, the

This Sheet Has Been Replaced

use of aqueous solutions of hydrogen peroxide to generate hydrogen peroxide vapor for sterilization may cause problems. At higher pressures, such as atmospheric pressure, excess water in the system can cause condensation. Thus, one must reduce the relative humidity in a sterilization enclosure before introducing the aqueous hydrogen peroxide vapor.

The sterilization of articles containing diffusion-restricted areas, such as long narrow lumens, presents a special challenge for hydrogen peroxide vapor that has been generated from an aqueous solution of hydrogen peroxide, because:

1. Water has a higher vapor pressure than hydrogen peroxide and will vaporize faster than hydrogen peroxide from an aqueous solution.

2. Water has a lower molecular weight than hydrogen peroxide and will diffuse faster than hydrogen peroxide in the vapor state.

Because of this, when an aqueous solution of hydrogen peroxide is vaporized, the water reaches the items to be sterilized first and in higher concentration. The water vapor therefore becomes a barrier to the penetration of hydrogen peroxide vapor into diffusion restricted areas, such as small crevices and long narrow lumens. One cannot solve the problem by removing water from the aqueous solution and using more concentrated hydrogen peroxide, since concentrated solutions of hydrogen peroxide, i.e., greater than 65% by weight, can be hazardous, due to the oxidizing nature of the solution.

U.S. Patents 4,642,165 and 4,744,951 attempt to solve this problem. The former discloses metering small increments of a hydrogen peroxide solution onto a heated surface to ensure that each increment is vaporized before the next increment is added. Although this helps to eliminate the difference in the vapor pressure and volatility between hydrogen peroxide and water, it does not address the fact that water diffuses faster than hydrogen peroxide in the vapor state.

The latter patent describes a process for concentrating hydrogen peroxide from a relatively dilute solution of hydrogen peroxide and water and supplying the concentrated hydrogen peroxide in vapor form to a sterilization

This Sheet Has Been Replaced

chamber. The process involves vaporizing a major portion of the water from the solution and removing the water vapor produced before injecting the concentrated hydrogen peroxide vapor into the sterilization chamber. The preferred range for the concentrated hydrogen peroxide solution is 50% to 80% by weight. This process has the disadvantage of working with solutions that are in the hazardous range; i.e., greater than 65% hydrogen peroxide, and also does not remove all of the water from the vapor state. Since water is still present in the solution, it will vaporize first, diffuse faster, and reach the items to be sterilized first. This effect will be especially pronounced in long narrow lumens.

U.S. Pat. 4,943,414 discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. This system has the advantage that the water and hydrogen peroxide vapor are pulled through the lumen by the pressure differential that exists, increasing the sterilization rate for lumens, but it has the disadvantage that the vessel needs to be attached to each lumen to be sterilized. In addition, water is vaporized faster and precedes the hydrogen peroxide vapor into the lumen.

U.S. Pat. No. 5,008,106 discloses that a substantially anhydrous complex of PVP and H_2O_2 is useful for reducing the microbial content of surfaces. The complex, in the form of a fine white powder, is used to form antimicrobial solutions, gels, ointments, etc. It can also be applied to gauze, cotton swabs, sponges and the like. The H_2O_2 is released upon contact with water present on the surfaces containing the microbes. Thus, this method too requires the presence of moisture to effect sterilization.

Certain inorganic hydrogen peroxide complexes have been reported including examples within the following classes: alkali metal and ammonium carbonates, alkali metal oxalates, alkali metal phosphates, alkali metal pyrophosphates, fluorides and hydroxides. U.S.S.R. patent document No. SU 1681860 (Nikolskaya et al.) discloses that surfaces can be decontaminated,

This Sheet Has Been Replaced

although not necessarily sterilized, using ammonium fluoride peroxohydrate ($NH_4F \cdot H_2O_2$). However, this inorganic peroxide complex provides decontamination only within the very narrow temperature range of 70-86°C. Even within this range, decontamination times were quite long, requiring at least two hours. Additionally, it is known that ammonium fluoride decomposes to ammonia and hydrofluoric acid at temperatures above 40°C. Due to its toxicity and reactivity, hydrofluoric acid is undesirable in most sterilization systems. Moreover, Nikolskaya et al. disclose that despite the release of 90% of its hydrogen peroxide at 60°C, $NH_4F \cdot H_2O_2$ is ineffective at decontamination of surfaces at this temperature. Thus, it appears that a factor other than hydrogen peroxide is responsible for the decontamination noted.

Hydrogen peroxide is capable of forming complexes with both organic and inorganic compounds. The binding in these complexes is attributed to hydrogen bonding between electron rich functional groups in the complexing compound and the peroxide hydrogen. The complexes have been used in commercial and industrial applications such as bleaching agents, disinfectants, sterilizing agents, oxidizing reagents in organic synthesis, and catalysts for free-radical-induced polymerization reactions.

Generally, these types of compounds have been prepared by the crystallization of the complex from an aqueous solution. For example, urea hydrogen peroxide complex was prepared by Lu et al. (*J. Am. Chem. Soc.* 63(1):1507-1513 (1941)) in the liquid phase by adding a solution of urea to a solution of hydrogen peroxide and allowing the complex to crystallize under the proper conditions. U.S. Pat. No. 2,986,448 describes the preparation of sodium carbonate hydrogen peroxide complex by treating a saturated aqueous solution of Na_2CO_3 with a solution of 50 to 90% H_2O_2 in a closed cyclic system at 0 to 5°C for 4 to 12 hours. More recently, U.S. Pat. No. 3,870,783 discloses the preparation of sodium carbonate hydrogen peroxide complex by reacting aqueous solutions of hydrogen peroxide and sodium carbonate in a batch or continuous crystallizer. The crystals are separated by filtration or centrifugation and the liquors used to produce more sodium carbonate solution. Titova et al.

This Sheet Has Been Replaced

(*Zhurnal Neorg. Khim.*, 30:2222-2227, 1985) describe the synthesis of potassium carbonate peroxyhydrate ($K_2CO_3 \cdot 3H_2O_2$) by reaction of solid potassium carbonate with an aqueous solution of hydrogen peroxide at low temperature followed by crystallization of the complex from ethanol. These methods work well for peroxide complexes that form stable, crystalline free-flowing products from aqueous solution.

U.S. Pat. Nos. 3,376,110 and 3,480,557 disclose the preparation of a complex of hydrogen peroxide with a polymeric N-vinylheterocyclic compound (PVP) from aqueous solution. The resultant complexes contained variable amounts of hydrogen peroxide and substantial amounts of water. U.S. Pat. No. 5,008,093 teaches that free-flowing, stable, substantially anhydrous complexes of PVP and H_2O_2 could be obtained by reacting a suspension of PVP and a solution of H_2O_2 in an anhydrous organic solvent like ethyl acetate. More recently, U.S. Pat. No. 5,077,047 describes a commercial process for producing the PVP-hydrogen peroxide product by adding finely divided droplets of a 30% to 80% by weight aqueous solution of hydrogen peroxide to a fluidized bed of PVP maintained at a temperature of ambient to 60°C. The resultant product was found to be a stable, substantially anhydrous, free flowing powder with a hydrogen peroxide concentration of 15 to 24%.

U.S. Pat. No. 5,030,380 describes the preparation of a solid polymeric electrolytic complex with hydrogen peroxide by first forming a complex in aqueous solution and then drying the reaction product under vacuum or by spray drying at a low enough temperature to avoid thermal degradation of the product.

All of these previous methods of preparing hydrogen peroxide complexes use solutions of hydrogen peroxide. Either the complex is formed in a solution containing hydrogen peroxide or droplets of a hydrogen peroxide solution are sprayed onto a fluidized bed of the reactant material.

Vapor phase and gas phase reactions are well known synthesis methods. For example, U.S. Pat. No. 2,812,244 discloses a solid-gas process for dehydrogenation, thermal cracking, and demethanation. Fujimoto et al. (*J.*

This Sheet Has Been Replaced

Catalysis, 133:370-382 (1992)) described a vapor-phase carboxylation of methanol. Zellers et al. (*Anal. Chem.*, 62:1222-1227 (1990)) discussed the reaction of styrene vapor with a square-plannar organoplatinum complex. These prior art vapor- and gas-phase reactions, however, were not used to form hydrogen peroxide complexes.

Summary of the Invention

One aspect of the present invention relates to an apparatus for hydrogen peroxide sterilization of an article. This apparatus includes a container for holding the article to be sterilized at a pressure of less than 50 torr. Preferably, the pressure is less than 20 torr, and more preferably less than 10 torr. The apparatus also includes a source of hydrogen peroxide vapor in fluid communication with the container. The source includes an inorganic hydrogen peroxide complex at a temperature greater than 86°C, and is configured so that the peroxide vapor can contact the article to effect sterilization. The source can be located within the container, or alternatively, the apparatus can include an enclosure disposed outside of the container in which the complex is located, and an inlet providing fluid communication betweeen the container and the enclosure, such that vapor released from the complex travels along the inlet and into the container to effect sterilization. The inorganic hydrogen peroxide complex can be a complex of sodium carbonate, potassium pyrophosphate or potassium oxalate. Preferably, the apparatus, also includes a heater located within the container, whereby the complex is placed on the heater and heated to facilitate the release of the vapor from the complex. Such a heater can be heated prior to contacting with the complex. The apparatus can also include a vacuum pump in fluid communication with the container for evacuating the container. In some embodiments, the apparatus includes an electrode adapated to generate a plasma around the article. Such an electrode can be inside the container, or can be spaced apart from the container and adapated to flow plasma generated thereby towards and around the article. In a preferred embodiment, the complex is in a solid phase.

This Sheet Has Been Replaced

Another aspect of the present invention relates to a method for hydrogen peroxide vapor sterilization of an article. This method includes placing the article into a container, and contacting the article with a hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex by heating the complex at a rate of at least 5°C/minute to contact and sterilize the article. Preferably, the heating rate is at least 10°C/minute, more preferably, at least 50°C/minute, and still more preferably at least 1000°C/minute. The complex preferably has less than 10% water. The complex can be heated, preferably to a temperature greater than 86°C to facilitate the release of the vapor from the complex. The container can be evacuated before introducing the vapor into the container at a pressure of less than 50 torr, more preferably less than 20 torr, and still more preferably less than 10 torr. Optionally, a plasma can be generated around the article after introducing the vapor into the container. The plasma can be generated either inside or outside of the container. The present invention also includes a method for hydrogen peroxide vapor sterilization of an article in which the inorganic hydrogen peroxide complex used is one which does not decompose to release a hydrohalic acid.

Yet another aspect of the present invention relates to a method for hydrogen peroxide sterilization of an article using a self-sterilizing enclosure. In this method, the article is placed in a enclosure containing an inorganic hydrogen peroxide complex, the enclosure is sealed, and the enclosure allowed to stand at a temperature below 70°C for a time sufficient to release hydrogen peroxide vapor from the complex and effect sterilization of the article. Although not necessary, the enclosure can be allowed to stand at a pressure less than atmospheric pressure or at a temperature above room temperature (23°C). Thus, the enclosure can be allowed to stand at a temperature below about 40°C. Any of a variety of enclosures can be used, e.g. a pouch, a container, a chamber or a room. Preferably, the hydrogen peroxide complex is in the form of a powder or tablet. The sealing step can include sealing the enclosure with a gas permeable material, such as TYVEK™, CSR wrap, or paper.

This Sheet Has Been Replaced

The present invention also relates to a sealed enclosure containing a sterile product and an inorganic hydrogen peroxide complex capable of releasing hydrogen peroxide vapor.

Included within the present invention is also a potassium pyrophosphate hydrogen peroxide complex.

A further aspect of the invention relates to a method for hydrogen peroxide sterilization of an article having an exterior and a narrow lumen therein. This method involves connecting a vessel containing an inorganic peroxide complex to the lumen of the article, placing the article within a container, whereby the vessel remains connected to the lumen, reducing the pressure within the container, and contacting the lumen of the article with hydrogen peroxide vapor released from the inorganic peroxide complex at a temperature less than 70°C.

Brief Description of the Drawings

FIGURE 1 is a schematic of a vapor sterilization apparatus of the present invention.

FIGURE 2 is a schematic of a vapor sterilization apparatus of the present invention which includes an electrode which is optionally used to generate plasma.

FIGURE 3A is a schematic of a device which can be used for heating peroxide complexes.

FIGURE 3B is a schematic of a preferred container for holding the peroxide source for sterilization according to the present invention.

FIGURE 4 is a graph depicting the release of hydrogen peroxide vapor from a vacuum unstable non-aqueous hydrogen peroxide complex.

FIGURE 5 is a schematic of a pressure control system of a differential scanning calorimeter (DSC) used to determine hydrogen peroxide release or decomposition properties of inorganic peroxide complexes according to the present invention.

FIGURE 6 is a graph showing the effect of pressure on hydrogen peroxide release from potassium oxalate peroxide complex.

This Sheet Has Been Replaced

FIGURE 7A is a schematic view of a bellows for injecting peroxide vapor into a chamber in accordance with the present invention before injection of the peroxide vapor.

FIGURE 7B is a schematic view of the bellows of FIGURE 7A showing a heated plate in contact with a peroxide complex during injection.

Detailed Description of the Invention

Hydrogen peroxide sterilizers that have been used in the past invariably used an aqueous solution of hydrogen peroxide as their source of sterilant. These sterilizers have disadvantages caused by the presence of water in the system. At higher pressure, such as atmospheric pressure, the excess water in the system can cause condensation. This requires that an extra step be performed to reduce the relative humidity of the atmosphere in an enclosure to be sterilized to an acceptable level before the aqueous hydrogen peroxide vapor is introduced. These sterilizers also have drawbacks caused by the facts that water, having a higher vapor pressure, vaporizes more quickly than hydrogen peroxide from an aqueous solution; and water, having a lower molecular weight, diffuses faster than hydrogen peroxide. When a medical device or the like is enclosed in a sterilizer, the initial sterilant that reaches the device from the hydrogen peroxide source is diluted in comparison to the concentration of the source. The dilute sterilant can be a barrier to sterilant that arrives later, particularly if the device being sterilized is an article, such as an endoscope, that has narrow lumens. Using a concentrated solution of hydrogen peroxide as the source in an attempt to overcome these drawbacks is unsatisfactory, because such solutions are hazardous.

In the present invention, the shortcomings of hydrogen peroxide sterilizers of the prior art are overcome by using a substantially non-aqueous (i.e., substantially anhydrous) source of hydrogen peroxide which releases a substantially non-aqueous hydrogen peroxide vapor. In a preferred embodiment, the substantially non-aqueous hydrogen peroxide vapor is produced directly from a substantially nonaqueous hydrogen peroxide complex. However, the substantially non-aqueous hydrogen peroxide vapor can also be

This Sheet Has Been Replaced

generated from an aqueous complex which is processed during vaporization to remove water, such as under vacuum. Thus, where an aqueous hydrogen peroxide complex is used, the aqueous complex can be converted to a substantially non-aqueous hydrogen peroxide complex while carrying out the process of the present invention. Preferably, the substantially non-aqueous hydrogen peroxide complexes contain less than about 20% water, more preferably no more than about 10% water, still more preferably no more than about 5% water, and most preferably no more than about 2% water.

As is apparent from the preferred percentages of water in the substantially non-aqueous hydrogen peroxide complexes used in the present invention, as provided above, the most preferred hydrogen peroxide complex and the peroxide vapor generated therefrom are substantially water-free. Nevertheless, as is also apparent from these figures, some water can be present in the system. Some of this water may derive from the decomposition of hydrogen peroxide to form water and oxygen as byproducts and some hydrogen binding of this water to the complex can occur.

The effect of water was measured in a series of tests, with a sterilization chamber maintained at various relative humidities. Test conditions were those described in Example 1, below, with spores supported on stainless steel (SS) blades in 3mm x 50cm stainless steel lumens. As shown in Table 2, under the test conditions, 5% relative humidity has no effect on efficacy but 10% relative humidity decreases the sterilization rate. This example shows that small amounts of moisture can be allowed in the system with the hydrogen peroxide generated from the non-aqueous peroxide complex and the presence of water in the system can be overcome by increasing the exposure time.

This Sheet Has Been Replaced

Table 2

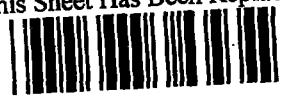
Effects of Relative Humidity on Efficacy SS Blades in 3mm x 50cm SS Lumens

Diffusion Time	Sterility Results (Positive/Samples)		
	1%RH	5%RH	10%RH
5	0/3	0/3	3/3
10	0/3	0/3	2/3
15	0/3	0/3	0/3
30	0/3	0/3	0/3

A primary criterion for the composition of the hydrogen peroxide source is the relationship between its stability and hydrogen peroxide evaporation rate as a function of temperature and pressure. Depending on the parameters of the sterilization process—e.g. pressure, temperature, etc.—a higher or lower peroxide evaporation rate may be preferred, and heating the peroxide source may or may not be required. The need for heating of the peroxide complex depends on the vapor pressure of the complex. Some peroxide complexes have a sufficiently high vapor pressure that a significant amount of hydrogen peroxide vapor can be released without heating the complex. In general, heating the complex increases the vapor pressure of hydrogen peroxide and accelerates the release of peroxide from the complex.

To provide a desirably high evaporation rate, the source should preferably have a large surface area. Thus the source may be a fine powder or a coating on a material that has a large surface area. Of course, safety, availability, and cost of the material are also important criteria. The release of hydrogen peroxide from hydrogen peroxide complexes with urea, polyvinylpyrrolidone, nylon-6, glycine anhydride, and 1,3 dimethyl urea were evaluated. The complexes of hydrogen peroxide with urea, polyvinylpyrrolidone, nylon-6, and glycine anhydride are solids. The 1,3 dimethyl urea peroxide complex is a liquid. The glycine anhydride hydrogen peroxide complex is a less stable complex under reduced pressure than the

This Sheet Has Been Replaced



other complexes evaluated, and under vacuum conditions, most of the hydrogen peroxide can be released from the complex without the need for additional heating.

Urea hydrogen peroxide complex is available in tablet form from Fluka Chemical Corp., Ronkonkoma, NY and in powder form from Aldrich Chemical Co., Milwaukee, WI. This complex is also known as urea peroxide, hydrogen peroxide urea complex, peroxide urea, peroxide urea adduct, urea peroxide adduct, percarbamide, carbamide perhydrate, and carbamide peroxide. As used herein, the term "urea peroxide" encompasses all of the foregoing terms.

The polyvinylpyrrolidone-hydrogen peroxide complex (PVP-H_2O_2) can be prepared by the method disclosed in International Application Pub. No. WO 92/17158. Alternatively, the complexes with PVP, with nylon-6, with 1,3 dimethylurea and with glycine anhydride, as well as with other organic and inorganic compounds can be prepared by the method disclosed in detail below.

Achieving suitable evaporation rates of anhydrous peroxide vapor from the source may be facilitated by elevated temperatures and/or reduced pressure. Thus, a heater for the peroxide source and/or a vacuum pump to evacuate the sterilization chamber are preferably a part of the sterilizer. Preferably, the source is covered with a layer of gas permeable material, such as TYVEK™ nonwoven polyethylene fabric, nonwoven polypropylene such as SPUNGUARD™, or similar material, which permits the peroxide vapor to pass but not the peroxide complexing material. Perforated aluminum or other suitable perforated material could also be used as a cover.

FIGURE 3A shows a device 80 that can be used to measure release of hydrogen peroxide from hydrogen peroxide complexes under various temperature conditions. In this device, an aluminum pan 90 is covered with a gas permeable layer 92, such as a layer of medical grade TYVEK™. The pan 90 is placed on top of a heating pad 94 which is placed in a pyrex pan 96. A thermocouple thermometer 98 is placed on the outside of the pan 90 approximately 1 cm from the bottom thereof.

This Sheet Has Been Replaced

A preferred container 99 for holding the peroxide source is illustrated in FIGURE 3B. The container 99 comprises a metal plate 100, e.g. an aluminum plate, with an optional attached heater used to heat the solid peroxide complex. A temperature monitor 101, such as a thermometer, can be placed on the plate 100 to monitor the temperature. The peroxide complex is placed directly on the plate 100. Alternatively, in order to provide even heating of all the peroxide complex, the peroxide complex can be placed between one or more aluminum screens 102, 104 placed on top of the plate 100. The aluminum screens 102, 104 provide greater surface area and even heating of the complex when larger amounts of peroxide complex are being used. The peroxide complex, or the screen or screens 102, 104, are then covered with a gas permeable layer 106, such as a layer of medical grade TYVEK™ or SPUNGUARD™, so that the hydrogen peroxide released from the complex passes through the covering 106 before diffusing into the rest of the chamber. A perforated aluminum plate 108 is optionally placed on top of the TYVEK™ or SPUNGUARD™ layer 106 to provide pressure to keep the complex in contact with the heated plate 100 and to ensure even heating of the peroxide complex.

The device just described provides even heating of the complex, which results in an increased amount of hydrogen peroxide vapor being released from the peroxide complex.

FIGURE 1 depicts a schematic of a hydrogen peroxide vapor sterilization apparatus of the present invention. Chamber 10 holds an article 12 which is to be sterilized and which, for convenience, is placed on shelf 14. Door 16 provides access to the interior of chamber 10. A non-aqueous source of hydrogen peroxide 18 is depicted on optional heater 20, which is controlled by temperature controller 22. The peroxide concentration can be monitored by optional monitor 24. If desired, chamber 10 can be evacuated using pump 26; however, sterilization can also be accomplished at atmospheric pressure.

The container that holds the articles to be sterilized can be a conventional sterilization chamber, which is evacuated, or it can be a container (or a room) at atmospheric pressure.

This Sheet Has Been Replaced

The time required to sterilize the articles depends on the nature, number and packaging of the articles and their placement in the chamber. Alternatively, it may be the chamber itself (or an entire room) that is being sterilized. In any case, optimum sterilization times can be determined empirically.

The use of pressure pulsing to enhance the penetration and antimicrobial activity of sterilant gases, which is well known in the sterilization art, can also be applied to the non-aqueous hydrogen peroxide process. As described in additional detail hereinbelow, plasma can also be used to further enhance activity.

At the conclusion of the sterilization process excess hydrogen peroxide can be removed from devices that have an affinity for peroxide by exchanging the air in contact with the devices. This can be accomplished by flowing warm air over the devices for an extended time or by evacuating the chamber.

Articles that have previously been sterilized by exposure to hydrogen peroxide vapor may also be exposed to the plasma to remove residual hydrogen peroxide that may remain on the articles. Since the hydrogen peroxide is decomposed into non-toxic products during the plasma treatment, the sterilized articles may be used without the need for any additional steps.

It may be desirable to isolate the peroxide source from the sterilizer after the peroxide vapor is released to avoid reabsorption of the vapor or, when a plasma is used, to avoid exposing the source to the plasma. Isolation is also advantageous when the complex used is not stable under vacuum. Isolation can be accomplished using valves or other isolating devices well known in the art.

FIGURE 2 depicts a schematic of a hydrogen peroxide plasma sterilization system of the present invention. Sterilization can be achieved with or without the use of plasma. The plasma can be used to enhance the sporicidal activity of the peroxide vapor, and/or to remove any residual hydrogen peroxide remaining on the sterilized articles.

This Sheet Has Been Replaced

Sterilization is carried out in chamber 30, which includes a door or opening 32 through which articles to be sterilized can be introduced. The chamber 30 includes an outlet 34 to a vacuum pump 36, through which the chamber can be evacuated. The outlet 34 contains a valve 38 to isolate the chamber from the vacuum pump 36. The chamber 30 also includes an inlet 40 attached to an enclosure 42 that contains the hydrogen peroxide complex. Inlet 40 contains a valve 44 that allows enclosure 42 to be isolated from the chamber. The sterilization system also contains an inlet 41 which connects the enclosure 42 and the vacuum pump 36, which contains a valve 43. This system allows the simultaneous evacuation of both enclosure 42 and chamber 30, or the independent evacuation of either enclosure 42 or chamber 30. Evacuation is controlled by the opening and closing of the valves 38, 44, and 43. As will be apparent to one having ordinary skill in the art, two pumps, one for each chamber, could also be employed in this system.

The enclosure 42 contains an optional heater 49 attached to a temperature controller 46 to control the temperature of the hydrogen peroxide complex. The hydrogen peroxide complex concentration in the vapor state can be monitored by an optional peroxide monitor 48. The interior of the chamber contains a radio frequency (RF) electrode 50, to which is attached a matching network 52 and an RF power supply 54. A convenient form for the electrode is a perforated cylinder, surrounding the samples and open at both end. The general operation of the present process is as follows:

1. The articles 56 to be sterilized are placed in the chamber 30.

2. The chamber 30 may be at atmospheric pressure or, alternatively, may be evacuated to facilitate penetration of the hydrogen peroxide. Evacuation is accomplished by opening valve 38 and turning on vacuum pump 36. Alternatively, both the chamber 30 and the enclosure 42 may be evacuated by opening valves 38 and 44, and/or 43.

3. The valves 38 and 43 are closed to isolate the vacuum pump 36 from the chamber 30 and enclosure 42, and the valve 44 is opened. Hydrogen peroxide vapor is delivered into chamber 30 from the hydrogen peroxide

This Sheet Has Been Replaced

source, which may be heated to facilitate the release of the hydrogen peroxide vapor. Optionally, air or an inert gas may also be added.

4. The articles 56 to be sterilized are either treated with peroxide vapor until sterilized or pretreated with peroxide vapor in the chamber 30 before plasma with sufficient power to sterilize is generated. If necessary, chamber 30 may be evacuated at this time to facilitate generation of the plasma. The duration of the pre-plasma holding period depends on the type of package used, the nature and number of items to be sterilized, and the placement of the items in the chamber. Optimum times can be determined empirically.

5. The articles 56 are subjected to a plasma by applying power from the RF power supply 54 to the RF electrode 50. The RF energy used to generate the plasma may be pulsed or continuous. The articles 56 remain in the plasma for a period to effect complete sterilization and/or to remove residual hydrogen peroxide. In certain embodiments, 5 to 30 minutes of plasma is used. However, optimum times can be determined empirically.

When used in the present specification and claims, the term "plasma" is intended to include any portion of the gas or vapor that contains electrons, ions, free radicals, dissociated and/or excited atoms or molecules produced as a result of an applied electric field, including any accompanying radiation that might be produced. The applied field may cover a broad frequency range; however, a radio frequency or microwaves are commonly used.

The non-aqueous hydrogen peroxide delivery system disclosed in the present invention can also be used with plasmas generated by the method disclosed in the previously mentioned U.S. Pat. 4,643,876. Alternatively, it may be used with plasmas described in U.S. Patent 5,115,166 or 5,087,418, in which the article to be sterilized is located in a chamber that is separated from the plasma source.

The device just described is particularly advantageous when using peroxide complexes that are not stable under vacuum. There are at least two possible methods that can be used to minimize the loss of hydrogen peroxide during the vacuum stage. First, the small chamber can be evacuated

This Sheet Has Been Replaced

independently. Second, if a small enough chamber is used, there is no need to evacuate the small chamber at all.

One such unstable non-aqueous peroxide complex is glycine anhydride-peroxide. This compound releases hydrogen peroxide vapor when placed under vacuum. FIGURE 4 is a graph illustrating the release of hydrogen peroxide vapor from glycine anhydride-peroxide complex under vacuum. The procedure used to release the hydrogen peroxide from the glycine anhydride complex is as follows: (1) The main chamber 30 was evacuated with valves 43 and 44 closed. (2) The chamber containing the hydrogen peroxide complex 42 was evacuated with valves 38 and 44 closed and valve 43 open. (3) Valve 43 was closed and valve 44 was opened and hydrogen peroxide vapor was allowed to diffuse into chamber 30.

As shown by the graph, hydrogen peroxide vapor is released from the complex as the pressure is reduced, even without additional heating. As illustrated in FIGURE 4, release of peroxide vapor is significantly increased by heating the complex to a higher temperature. Thus, even unstable peroxide complexes are useful in the sterilization method of the present invention.

The present invention provides at least four advantages over earlier hydrogen peroxide sterilization systems:

1. The use of concentrated, potentially hazardous hydrogen peroxide solutions is circumvented.

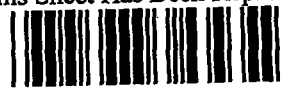
2. The need to reduce beforehand the relative humidity of areas to be sterilized in order to prevent condensation is eliminated.

3. Water is substantially eliminated from the system, so that there is little competition between water and hydrogen peroxide for diffusion into long narrow lumens.

4. The need to attach a special vessel to deliver sterilant gases into long narrow lumens can often be eliminated.

That sterilization can be effected using hydrogen peroxide vapor in the substantial absence of moisture is one of the surprising discoveries of the present invention. The prior art teaches that the presence of water is required

This Sheet Has Been Replaced



to achieve sterilization in chemical gas or vapor state sterilization processes. Advantageously, the present invention substantially eliminates water from the system, which results in faster, more efficient and effective sterilization.

The sterilization efficacy of various non-aqueous hydrogen peroxide complexes was determined as described below in Examples 1-4.

Example 1

Efficacy data was obtained with hydrogen peroxide vapor released from substantially anhydrous urea peroxide complex using *Bacillus subtilis* var. *(niger)* spores in metal and TEFLON™ plastic lumens as the biological challenge.

A. Test Procedures

1. Equipment

Four grams of crushed hydrogen peroxide urea adduct tablet (Fluka Chemical Corp, Ronkonkoma, NY) were placed in an aluminum pan 90, as described in FIGURE 3A. The top of the pan 90 was covered with medical grade TYVEK™ 92 (a breathable spunbond polyethylene fabric) so that any hydrogen peroxide released from the complex would need to pass through the TYVEK™ covering before diffusing into the rest of the chamber. The aluminum pan 90 was placed on a heating pad 94 in a pyrex dish 96 located in the bottom of an aluminum sterilization chamber (see FIGURE 1). The sterilization chamber, which had an approximate volume of 173 liters, also contained:

- A hydrogen peroxide monitor for measuring hydrogen peroxide concentration in the vapor phase.
- A temperature controller for controlling the temperature of the heating pad.
- An injection port through which liquid hydrogen peroxide could be injected into the chamber.
- A metal shelf on which a plastic tray containing lumen devices were placed for testing.

This Sheet Has Been Replaced

- Electrical resistance heaters on the exterior of the chamber walls, which maintained the chamber temperature at 45°C during the efficacy testings.

2. **Biological Challenge and Test**

To evaluate the efficacy of the non-aqueous peroxide delivery system, a biological challenge consisting of 1.04×10^6 *B. subtilis* var. *(niger)* spores on a stainless steel scalpel blade was placed equally distant from each end of the stainless steel lumens of dimensions 3mm ID × 40cm length, 3mm ID × 50cm length, and 1mm ID × 50cm length. These ID's and lengths are typical for metal lumens used in medical devices. The compartment in the middle of each lumen that contained the biological test piece had the dimensions 13mm ID × 7.6cm length. In the biological testing with metal lumens, a total of 9 lumens were evaluated per test. These included 3 lumens from each of the 3 different sets of ID's and lengths available.

Similar tests were conducted with a biological challenge consisting of 4.1×10^5 *B. subtilis* var. *(niger)* spores on a paper strip (6mm × 4mm Whatman #1 chromatography paper) located equally distant from the ends of TEFLON™ lumens of dimensions 1mm ID × 1 meter length, 1mm ID × 2 meter length, 1mm ID × 3 meter length, and 1mm ID × 4 meter length. The center compartment of these lumens that contained the biological test piece had the dimensions 15mm ID × 7.6cm length. In the biological testing with TEFLON™ lumens, a total of 12 lumens were evaluated per test, 3 lumens from each of the 4 different lengths available.

The lumens containing the biological test samples were placed in a plastic tray that was then placed on the shelf in the sterilization chamber. The chamber door was then closed and the chamber evacuated to 0.2 Torr pressure with a vacuum pump. The aluminum pan containing the hydrogen peroxide urea adduct was then heated to 80 to 81°C for a period of 5 minutes, as measured by a thermocouple thermometer placed on the side wall of the aluminum pan approximately 1 cm from the bottom of the pan. During this time

This Sheet Has Been Replaced

the concentration of hydrogen peroxide in the chamber increased to 6mg/L as measured by the peroxide monitor.

The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5, 10, 15, 20, and 25 minutes. After exposure to the hydrogen peroxide vapor, the biological test samples were aseptically transferred into 15mL of trypticase soy broth containing 277 units of catalase to neutralize any hydrogen peroxide residuals that may remain on the test samples. All samples were incubated for 7 days at 32°C and observed for growth.

Comparative studies were also conducted in which a 50% aqueous solution of hydrogen peroxide was injected into the sterilization chamber and vaporized from a heated injector (a heated metal surface). The volume of hydrogen peroxide solution injected produced a vapor phase concentration of hydrogen peroxide of 6mg/L. The test lumens and biological test samples used in these tests were identical to those used in the non-aqueous hydrogen peroxide tests. The handling of the biological test samples after exposure to the hydrogen peroxide was also identical.

B. Test Results

The results of these tests with stainless steel and TEFLON™ lumens, which are presented in Tables 3 and 4, respectively, illustrate the advantages of the non-aqueous peroxide delivery system with both metal and non-metal lumens. Total kill of the bacterial spores was achieved within 5 minutes with the non-aqueous peroxide delivery system for the smallest ID and the longest lumens evaluated. At the same time, total kill was not achieved even after 25 minutes of diffusion time with the 50% hydrogen peroxide solution.

This Sheet Has Been Replaced

Table 3

Aqueous/Non-Aqueous Efficacy Comparison
SS Blades in SS Lumens

SOURCE OF PEROXIDE	DIFFUSION TIME (MIN)	STERILITY RESULTS (POSITIVE/SAMPLES) 3mm x 40cm	3mm x 50cm	1mm x 50cm
50% SOLUTION	5	3/3	3/3	3/3
	10	0/3	2/3	3/3
	15	1/3	1/3	1/3
	20	0/3	0/3	1/3
	25	0/3	0/3	1/3
UREA PEROXIDE	5	0/3	0/3	0/3
	10	0/3	0/3	0/3
	15	0/3	0/3	0/3
	20	0/3	0/3	0/3
	25	0/3	0/3	0/3

This Sheet Has Been Replaced

Table 4

Aqueous/Non-Aqueous Efficacy Comparison
6mm x 4mm Paper strip in TEFLON™ Lumens

SOURCE OF PEROXIDE	DIFFUSION TIME (MIN)	STERILITY RESULTS (POSITIVE/SAMPLES) 1mm x 1m	1mm x 2m	1mm x 3m	1mm x 4m
	5	3/3	3/3	3/3	3/3
	10	3/3	3/3	3/3	3/3
50% SOLUTION	15	0/3	1/3	1/3	2/3
	20	0/3	0/3	1/3	1/3
	25	0/3	0/3	0/3	1/3
	5	0/3	0/3	0/3	0/3
UREA	10	0/3	0/3	0/3	0/3
PEROXIDE	15	0/3	0/3	0/3	0/3
	20	0/3	0/3	0/3	0/3
	25	0/3	0/3	0/3	0/3

The fact that rapid sterilization can be accomplished in the absence of substantial amounts of water is surprising, in light of the fact that moisture has generally been present during chemical gas/vapor phase sterilization by various sterilants other than hydrogen peroxide. Since vapor phase hydrogen peroxide sterilization systems have used aqueous solutions of hydrogen peroxide, there has been moisture present in those systems as well.

To test the sterilization efficacy of various other peroxide complexes, the following experiments were performed.

Examples 2, 3 and 4

The apparatus of Example 1 was used to test the efficacy of polyvinylpyrrolidone-hydrogen peroxide complex (Example 2), nylon 6-hydrogen peroxide complex (Example 3), and 1,3 dimethylurea hydrogen peroxide complex (Example 4). These compounds were synthesized according to the

This Sheet Has Been Replaced

method disclosed below in Examples 12 and 13. Test parameters were as follows:

	Example		
	2	3	4
Chamber Temp.	45°C	45°C	45°C
Initial Pressure	0.2 Torr	1.0 Torr	1.0 Torr
Wt. % of peroxide	17%	10.5%	26.6%
Peroxide concentration	6mg/L	6mg/L	6mg/L
Wt. of complex used per cycle	8g	18g	6g
Temp to release peroxide	110°C	110°C	80°C

In each case, spore supports were 6mm × 4mm paper substrates in plastic lumens and stainless steel blades in stainless steel lumens. The results of this efficacy testing appear below in Table 5.

Table 5

Efficacy of Complexes with PVP, nylon 6, and 1,3-dimethylurea

		STERILITY RESULTS (POSITIVE/SAMPLES) With 5 Minutes Exposure		
TYPE OF LUMEN	SIZE OF LUMENS	Example 2	Example 3	Example 4
TEFLON™	1mm × 1m	0/3	0/3	0/3
	1mm × 2m	0/3	0/3	0/3
	1mm × 3m	0/3	0/3	0/3
	1mm × 4m	0/3	0/3	0/3
STAINLESS STEEL	3mm × 40cm	0/3	0/3	0/3
	3mm × 50cm	0/3	0/3	0/3
	1mm × 50cm	0/3	0/3	0/3

This Sheet Has Been Replaced

The results appearing in Table 5 show that each of the tested hydrogen peroxide complexes generate peroxide vapor which provides efficient sterilization after only five minutes exposure.

The temperature required to release the hydrogen peroxide vapor from the solid complex which is shown above is the temperature measured by a thermocouple thermometer located on the outside of the aluminum pan approximately 1 cm from the bottom of the pan. Further testing using a thermometer, such as a fluoroptic thermometer, placed on the inside bottom of the pan indicated that the temperature at the bottom of the pan was approximately 30-35°C higher, as described in Example 5 below. Thus, in the previous example, the temperature at the bottom of the pan was approximately 110 -115°C when the thermocouple thermometer read 80°C, and the temperature at the bottom of the pan was approximately 140 -145°C when the thermocouple thermometer read 110°C.

Example 5

To determine the temperature at the bottom of the aluminum pan used to contain the solid peroxide complex, a fluoroptic thermometer was taped to the inside bottom of the aluminum pan. An Omega™ thermocouple thermometer was placed on the outside of the aluminum pan approximately 1 cm from the bottom of the pan. Three different readings of the thermometers were taken. Each time the pan was heated to the desired temperature indicated by the thermometer placed on the side of the pan, allowed to cool, and then re-heated to the desired temperature. The recorded temperatures are listed below:

Temp. at side of pan	Temp. at bottom of pan (°C) 1st	2nd	3rd	avg
80°C	110.9	110.6	110.6	110.7
100°C	131.5	132.6	132.0	132.0

This Sheet Has Been Replaced

The results show that the temperature at the bottom of the aluminum pan was approximately 30-35°C higher than the temperature indicated by the thermocouple thermometer located at the side of the pan.

Further testing was performed to compare the efficacy data obtained using an aqueous and non-aqueous source of peroxide in an open (non-lumen) system. The experiments are described in detail below.

Example 6

The apparatus of Example 1 was used with a biological challenge that consisted of 6.8×10^5 *B. subtilis* var *(niger)* spores on a 6mm × 4mm strip of Whatman #1 chromatography paper packaged in a TYVEK™/MYLAR™ envelope. (TYVEK™ is a gas permeable fabric made of polyethylene. MYLAR™ is a non-gas permeable polyester material). Packaged biological challenge strips were placed in the front, middle and back of a polyphenylene oxide tray that contained a flexible fiberoptic sigmoidoscope. The tray was placed in a polyphenylene oxide container that had one port in the top and two ports in the bottom to allow for diffusion. The four-inch diameter ports were covered with a breathable polypropylene packaging material (SPUNGUARD™ Heavy Duty Sterilization Wrap, Kimberly-Clark, Dallas, TX) to maintain the sterility of the contents of the container after sterilization. The container was placed in the apparatus of Example 1 and the pressure in the chamber was reduced to 0.2 Torr. The aluminum pan containing 2 grams of hydrogen peroxide urea adduct (Fluka Chemical Corp.) was then heated to 80 to 81°C, as measured by a thermocouple thermometer placed on the outside of the aluminum pan approximately 1 cm from the bottom of the aluminum pan, for 5 minutes to provide 3mg/L of hydrogen peroxide vapor in the chamber. The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5 and 10 minutes. After exposure the test samples were handled in the same way as were those in Example 1.

Comparative studies were also conducted in which a 50% aqueous solution of hydrogen peroxide was injected into the sterilization chamber and vaporized from a heated injector. The volume of hydrogen peroxide solution

This Sheet Has Been Replaced

injected produced a vapor phase concentration of 3mg/L. The test configuration, the composition of the biological test samples, and the handling of the biological test samples after exposure were all identical to those used in the non-aqueous hydrogen peroxide tests. The results of these tests are presented in Table 6.

Table 6

Aqueous/Non-Aqueous Efficacy Comparison in Open System (Non-Lumen Test)

Source of Peroxide	Diffusion Time (min)	Sterility Results (positive/samples)
50% solution	5	3/3
	10	3/3
Urea Peroxide	5	1/3
	10	0/3

The results of these tests demonstrate the greater efficacy of the non-aqueous when compared with the aqueous hydrogen peroxide process in an "open" system in which the biological sample was not placed in a lumen. Again, it was surprisingly discovered that a non-aqueous system provided superior sterilization even when diffusion of hydrogen peroxide into a long and narrow lumen is not required. This suggests that the mode of action of hydrogen peroxide is not the same for systems with and without water.

Further testing was performed to determine the efficacy a non-aqueous peroxide vapor at normal, not reduced, pressure. This testing is detailed below.

Example 7

Efficacy tests were conducted with the hydrogen peroxide vapor released from the urea peroxide complex in an open system at atmospheric pressure. In this test the biological challenge of 1.04×10^6 *B. subtilis* var. *(niger)* spores on the stainless steel surgical blades were packaged in a TYVEK™/MYLAR™

This Sheet Has Been Replaced

envelope. Packaged biological challenge blades were placed on the front, middle, and back of a polyphenylene oxide tray. The tray was placed in the apparatus of Example 1 and the chamber door was closed. The aluminum pan containing 4.0 gm of urea peroxide (Fluka Chemical Corp.) was heated to 80° to 81°C, as measured by a thermocouple thermometer placed on the side of the aluminum pan approximately 1 cm from the bottom of the pan, for the duration of the test. The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5, 10, 20 and 30 minutes. After exposure the test samples were handled the same way as those in Example 1. The results of these tests are presented in Table 7 and demonstrate the efficacy of the non-aqueous peroxide process in an open system at atmospheric pressure.

Table 7

Efficacy of non-aqueous peroxide process in open system at atmospheric pressure

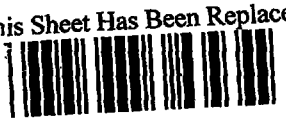
Source of Peroxide	Diffusion Time (minutes)	Sterility Results (positive/samples)
Urea Peroxide	5	3/3
	10	1/3
	20	0/3
	30	0/3

Further tests were conducted to determine the approximate amount of peroxide released from the hydrogen peroxide urea complex at various temperatures. This testing is described in Example 8.

Example 8

Urea peroxide powder, obtained from crushing the commercially available tablets (Fluka Chemical Corp.), was placed between two aluminum screens in an apparatus according to FIGURE 3B having dimensions 12.7 cm

This Sheet Has Been Replaced



× 12.7 cm. The aluminum plate was then heated and the temperature was monitored using a thermometer located near a corner of the aluminum plate. Table 8 lists the approximate percent of peroxide released at various temperatures after heating for five minutes. The data show that approximately 100% of the peroxide is released from the complex at a temperature of 140°C. Lesser percentages of peroxide are released at lower temperatures.

Table 8

Release of non-aqueous peroxide at various temperatures

Heating Temperature	% Peroxide Released
80°C	~25%
100°C	~65%
120°C	~80%
130°C	~90%
140°C	~100%

Peroxide complexes having the ability to release hydrogen peroxide vapor at room temperature and atmospheric pressure, such as the urea peroxide complex, allows them to be effective for use in various sterilization applications. Not only can they be used in the sterilization apparatus of the present invention described above, the compounds of the present invention can also be used as part of self-sterilizing packaging materials, or applied onto supports such as gauze, sponge, cotton, and the like. The compounds allow for sterilization of sealed packages at room temperature or at elevated temperatures, and are particularly useful for the sterilization of packaged medical or surgical products.

Particular uses of the compounds of the present invention are described in the examples which follow. The peroxide complex used in the following

This Sheet Has Been Replaced

examples was urea peroxide in the form of a tablet (Fluka Chemical Corp.) or in the form of a powder obtained by crushing the tablets.

Example 9

A self-sterilizing pouch was assembled as follows: A surgical scalpel having 3.8×10^5 *B. subtilis* var. *niger* spores on its surface was placed in a sterile petri dish. The dish was placed in a larger petri dish, together with 1 gm urea peroxide complex in either tablet or powder form. The larger petri dish was then inserted into a pouch formed of TYVEK™/MYLAR™ (gas permeable, Table 9), MYLAR™/MYLAR™ (non-gas permeable, Table 10) or Paper/MYLAR™ (gas permeable, Table 10). The pouch was then sealed.

Each pouch was exposed to various temperatures for various time periods, as shown in Tables 9 and 10 below. The biological test samples were evaluated for sterilization as described in Example 1. The results are included in Tables 9 and 10, with a "+" sign indicating bacterial growth.

Table 9
Self-Sterilizing Pouches
With Breathable Barrier (TYVEK™/MYLAR™)

Temperature	Peroxide Type	1 hr.	2 hr.	3 hr.	4 hr.
23°C	powder	+	-	-	-
	tablet	+	+	-	-
40°C	powder	-	-	-	-
	tablet	-	-	-	-
60°C	powder	-	-	-	-
	tablet	-	-	-	-

Table 10 lists the efficacy data for self-sterilizing pouches with (Paper/MYLAR™) and without (MYLAR™/MYLAR™) a breathable barrier. The pouches were assembled as described above, however the peroxide vapor source was urea peroxide in powder form only.

This Sheet Has Been Replaced

Table 10
Self-Sterilizing Pouches With & Without Breathable Barrier

Temperature	Packaging Type	2 hr.	4 hr.
23°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	+	-
40°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	-	-
60°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	-	-

Results from this testing show that the urea peroxide complex of the present invention included in a pouch with and without a breathable barrier provides effective sterilization to an article inside the pouch in the absence of moisture at room temperature and atmospheric pressure after only 2 to 3 hours. At higher temperatures, sterilization is effected after only one hour.

To determine the efficacy of the sterilization system of the present invention in a closed container, the following experiment was performed.

Example 10

A self-sterilizing container was assembled as follows: A stainless steel support having either 3.8×10^5 *B. subtilis* var. *niger* spores on its surface (Table 11) or having 9.2×10^5 *B. subtilis* var. *niger* spores on its surface (Table 12), was placed inside a small polyethylene (PE) vial having 20 holes (3/16" in size) in its surface. The vial was placed in a larger PE vial, which was covered with either an air tight cap, or a gas permeable layer of SPUNGUARD® (CSR Wrap). Also included in the larger vial was a second PE vial, also having 20 holes (3/16" in size) in its surface. This vial contained 1 gm urea peroxide in either powder or tablet form, and was sealed in either a SPUNGUARD™ (CSR wrap) or TYVEK™ pouch.

Each container was exposed to various temperatures for various time periods, as shown in Tables 11 and 12 below. The biological test samples

This Sheet Has Been Replaced

were evaluated for sterilization as described in Example 1. The results are included in Tables 11 and 12, with a "+" sign indicating bacterial growth.

Table 11
Self-Sterilizing Containers Without Breathable Window

Temperature	Packaging Type	2 hr.	6 hr.
23°C	Unpackaged tablet	+	-
	C/C* packaged tablet	+	-
	C/C packaged powder	+	-
40°C	Unpackaged tablet	-	-
	C/C packaged tablet	-	-
	C/C packaged powder	-	-
60°C	Unpackaged tablet	-	-
	C/C packaged tablet	-	-
	C/C packaged powder	-	-

* - pouch formed from CSR wrap

This Sheet Has Been Replaced

Table 12
Self-Sterilizing Containers With Breathable CSR Window

Temperature	Packaging Type	0.5 hr.	1.0 hr.	1.5 hr.	2.0 hr.	3.0 hr.	4.0 hr.
23°C	Unpackaged tablet		+	+	+	-	-
	Unpackaged powder		+	+	+	-	-
	T/T* packaged tablet		+	+	+	+	-
	T/T packaged powder		+	+	+	-	-
	C/C** packaged tablet		+	+	+	-	-
	C/C packaged powder		+	+	+	-	-
40°C	Unpackaged tablet	-	-	-	-		
	Unpackaged powder	-	-	-	-		
	T/T packaged tablet	+	-	-	-		
	T/T packaged powder	-	-	-	-		
	C/C packaged tablet	-	-	-	-		
	C/C packaged powder	-	-	-	-		
60°C	Unpackaged tablet	-	-	-	-		
	Unpackaged powder	-	-	-	-		
	T/T packaged tablet	-	-	-	-		
	T/T packaged powder	-	-	-	-		
	C/C packaged tablet	-	-	-	-		
	C/C packaged powder	-	-	-	-		

* - pouch formed from TYVEK™
** - pouch formed from CSR wrap

Results from this testing show that the non-aqueous urea peroxide complex included in a container with and without a breathable barrier provides effective sterilization at room temperature after only 3-4 hours. At higher temperatures, sterilization is effected after as little as one half hour.

The non-aqueous peroxide complexes which release peroxide vapor have been found to be useful in the sterilization of articles at room temperature, and more effectively, at higher temperatures. These complexes can be placed in a pouch, container, chamber, room or any area capable of being sealed, where they release peroxide vapor which effectively sterilizes the articles. The complexes can be heated to facilitate the release of vapor, and to provide

This Sheet Has Been Replaced

sterilization in less time than that required for room temperature sterilization. The compounds of the present invention are therefore useful in a variety of applications where sterilization is desired. Simply by placing the complex in a sealed area containing an article or articles to be sterilized, sterilization can be achieved. By contrast with prior art methods, there is no need for contact with moisture to provide activation of the hydrogen peroxide.

To confirm that sterilization can be effected using non-aqueous peroxide complexes in less time at lower pressures, the following experiment was performed.

Example 11

A self-sterilizing container was assembled as follows: A stainless steel support having 9.2×10^5 *B. subtilis* var. *niger* spores on its surface was placed inside a small PE vial having 20 holes (3/16" in size) in its surface. The vial was placed in a larger PE vial, which was covered with a gas permeable layer of CSR wrap (SPUNGUARD™). Also included in the larger vial was a second PE vial, also having 20 holes (3/16" in size) in its surface. This vial contained 1 gm urea peroxide in either powder or tablet form. The vial was then sealed in a CSR wrap or TYVEK™ pouch.

The large vials were placed in either a 4.5 L sterilization chamber or a 173 L sterilization chamber. Each container was exposed to 100 torr pressure and 23°C temperature for 2 hours, as shown in Table 13. The biological test samples were evaluated for sterilization as described in Example 1. The results are included in Table 13.

Table 13
Self-Sterilizing Containers With Breathable Window In Reduced Pressure Conditions

Temperature	Packaging Type	4.5 L chamber	173 L chamber
23°C	Unpackaged powder	-	-
	T/T packaged powder	-	-
	C/C packaged powder	-	-

This Sheet Has Been Replaced

These results show that non-aqueous urea peroxide complex included in a container with a breathable barrier provides effective sterilization at 100 torr and room temperature after only 2 hours. These results, when compared with the results in Table 12, demonstrate that the peroxide complexes of the present invention provide sterilization at reduced pressures in less time than that required to effect sterilization at atmospheric pressure.

Thus, the hydrogen peroxide complexes of the present invention can provide effective sterilization in significantly shorter periods of time. In addition, as discussed above, plasma can also be used to enhance the sterilization activity of the hydrogen peroxide vapor. The articles to be sterilized are subjected to a plasma after exposure to the peroxide vapor, and remain in the plasma for a period of time sufficient to effect complete sterilization.

Articles that have been sterilized by exposure to hydrogen peroxide vapor can be exposed to a plasma to remove any residual hydrogen peroxide remaining on the articles. Because the residual hydrogen peroxide is decomposed into non-toxic products during the plasma treatment, the sterilized articles are ready for use following treatment, without the need for any additional steps.

Non-aqueous peroxide complexes are useful in a variety of applications, including as a component of self-sterilizing packaging. In addition, the complexes are suitable for use in various methods for vapor sterilization of articles, such as the method disclosed in U.S. Patent No. 4,943,414. This patent discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. The method disclosed in the patent can be modified to allow for use of a non-aqueous peroxide compound. The compound is placed in a vessel and connected to the lumen of the article to be sterilized. The article is then placed within a container and the container evacuated. The lumen of the article and the exterior of the article are contacted by the hydrogen peroxide vapor released from the non-aqueous

This Sheet Has Been Replaced

compound. A plasma can optionally be generated and used to enhance sterilization and/or to remove any residual hydrogen peroxide form the article.

Use of non-aqueous peroxide complexes in the system just described overcomes the disadvantage that the water in the aqueous solution is vaporized faster and precedes the hydrogen peroxide vapor into the lumen. Thus, more effective sterilization is achieved and less time is required to effect sterilization. Hydrogen peroxide complexes such as glycine anhydride are especially advantageous since they release a significant amount of hydrogen peroxide at reduced pressure without the need for additional heating of the complex.

Synthesis of Non-Aqueous Hydrogen Peroxide Complexes

The present invention further provides a process for preparing non-aqueous hydrogen peroxide complexes that are useful as the source in a hydrogen peroxide vapor sterilizer, or as a component of self-sterilizing packaging, as was described above. Of course, the hydrogen peroxide complexes can be used for other applications, such as for bleaching agents, contact lens solutions, catalysts, and other applications which will be well known by those having ordinary skill in the art.

The general procedure for preparing the hydrogen peroxide complexes of this invention is as follows:

(1) Place the reactant material in the chamber.

The material to be reacted with the hydrogen peroxide can be a solid in various forms, (e.g., powder, crystal, film etc., preferably having high surface area to increase the reaction rate). The reactant material can also be present as a solution in water or another solvent, if sufficient time is allowed to evaporate the solvent after the pressure is reduced in the chamber. The material may also be a liquid whose boiling point is higher than that of hydrogen peroxide (150°C). Since reaction rates are faster at elevated temperature, the chamber is preferably heated whether before or after the reactant composition is introduced. However, the temperature should not be so high that the reactant boils or vaporizes.

This Sheet Has Been Replaced

The reactant composition may be contained in any container that provides access to the peroxide vapor. If it is in the form of a powder or other form that may be blown about when the chamber is evacuated, then the reactant may be retained in a permeable container, which allows hydrogen peroxide to diffuse into the container.

(2) Evacuate the chamber.

Preferably, the chamber is evacuated to a pressure that is below the vapor pressure of the hydrogen peroxide (which depends on its concentration and temperature), in order to assure that all of the peroxide is in the vapor phase. The vapor pressure increases with increasing temperature and decreases with increasing peroxide concentration. For most of the experiments, the chamber was evacuated to about 0.2 Torr and the temperature was ambient or above.

(3) Generate hydrogen peroxide vapor.

The hydrogen peroxide vapor can be generated from a hydrogen peroxide solution or from a substantially anhydrous hydrogen peroxide complex. The latter yields dry hydrogen peroxide in the vapor state, which is an advantage if either the material to be reacted with the vapor or the complex to be formed is hygroscopic. Another advantage of generating the hydrogen peroxide vapor from a substantially water-free complex is that the percent of hydrogen peroxide in the complex being formed is higher than if the vapor is generated from an aqueous solution of H_2O_2. This is probably due to the competition between water molecules and H_2O_2 molecules for bonding sites on the complex when an aqueous solution is used to generate the H_2O_2 vapor.

The peroxide vapor can be generated within the same chamber that houses the reactant material or in another chamber separated from it by a vacuum valve.

(4) React the reactant material with hydrogen peroxide.

The time required for the reaction depends, of course, on the reaction rate of the reactant with hydrogen peroxide. It can be empirically determined by monitoring the pressure, which decreases during the binding of peroxide to

This Sheet Has Been Replaced

the reactant material. Typically, the reaction time is about 5-30 minutes. The concentration of vaporized hydrogen peroxide and the weight of the starting material determine the weight percentage of peroxide in the final reaction product. As the weight ratio of reactant to hydrogen peroxide increases, the weight percentage of hydrogen peroxide in the complex decreases. The reaction can be repeated multiple times to increase the concentration of hydrogen peroxide in the complex.

(5) Evacuate the chamber again.

At the end of the reaction period, the chamber is further evacuated to about 2 Torr to remove any unreacted hydrogen peroxide.

(6) Vent the chamber and retrieve the hydrogen peroxide complex.

The mechanism by which the hydrogen peroxide forms a complex with the reactant material is not completely understood. The formation of the complex is believed to involve hydrogen bond formation between the hydrogen peroxide and electron-rich functional groups containing oxygen and/or nitrogen on the reactant material. It is not known if this is the only mode of binding; however, materials with a wide range of functional groups have been found to form complexes with hydrogen peroxide.

The advantages of the vapor phase reaction over earlier methods of hydrogen peroxide complex formation include:

1. The ratio of hydrogen peroxide to reactant material can be accurately controlled by varying the amount of hydrogen peroxide present in the vapor state or the amount of reactant material exposed to the vapor.

2. The need to remove solvent from the reaction product is eliminated.

3. Peroxide complexes can be formed that are liquid or solids, such as powders, crystals, films, etc.

4. Peroxide complexes of hygroscopic materials can be prepared.

The synthesis of the non-aqueous peroxide complexes according to the present invention is further described in the following examples. Many of these compounds have utility as catalysts, in addition to having the utilities described

This Sheet Has Been Replaced

in greater detail herein, as will be readily appreciated by those having ordinary skill in the art. The examples represent embodiments of the compositions and processes of the invention, but they are not in any way intended to limit the scope of the invention.

Example 12

A hydrogen peroxide complex of glycine anhydride was prepared as follows: A 1.0 gram sample of glycine anhydride (Aldrich Chemical Co., Milwaukee, WI) was placed in an aluminum tray in a 173 liter chamber maintained at a temperature of 45°C. The top of the aluminum tray was covered with TYVEK™ nonwoven fabric, which prevented the glycine anhydride from coming out of the tray when the pressure in the chamber was reduced but was breathable and did not absorb hydrogen peroxide. The chamber door was closed and the pressure in the chamber was reduced to 0.2 Torr by evacuating the chamber with a vacuum pump. A hydrogen peroxide concentration of 10 mg/liter was created by evaporation of an appropriate volume of a 70% aqueous solution of hydrogen peroxide (FMC Corp., Philadelphia, PA) into the chamber. The hydrogen peroxide vapor was maintained in contact with the glycine anhydride for 20 minutes. At the end of the reaction period, the chamber pressure was reduced to 2 Torr and then returned to atmospheric pressure. The reaction product was removed from the chamber and analyzed for weight percent hydrogen peroxide by the following iodometric titration reactions.

$$H_2O_2 + 2KI + H_2SO_4 \longrightarrow I_2 + K_2SO_4 + 2H_2O$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$

A starch indicator was used in the iodine-sodium thiosulfate titration reaction to enhance the color change at the end point. The percentage by weight of hydrogen peroxide was calculated by the following equation:

wt% H_2O_2 = [(ml of $Na_2S_2O_3$)*(normality of $Na_2S_2O_3$) *1.7]/(sample weight in grams)

The weight percentage of hydrogen peroxide in the glycine anhydride complex was found to be 24.3%.

This Sheet Has Been Replaced

Example 13

The hydrogen peroxide complexes of a wide variety of organic and inorganic complexes were prepared using the procedure of Example 12. In each case, the reaction conditions were the same as those in Example 12, except 1.0 gram of each one of the compounds presented in Table 14 was used in place of glycine anhydride.

This Sheet Has Been Replaced

Table 14

COMPOUNDS EVALUATED AND WEIGHT PERCENT HYDROGEN PEROXIDE PRESENT IN COMPLEXES FORMED BY VAPOR PHASE SYNTHESIS PROCESS

Chemical Name	Chemical Structure	Wt% After Peroxide Treatment	Category
Poly(vinyl alcohol)	$[-CH_2CH(OH)-]_n$	18.9%	Alcohol
Poly(vinyl methyl ether)	$[-CH_2CH(OCH_3)-]_n$	22.0%	Ether
Poly(vinyl methyl Ketone)	$[-CH_2-CH(COCH_3)-]_n$	13.9%	Ketone
Poly(acrylic acid)	$[-CH_2CH(COOH)-]_n$	5.1%	Acid
Glycine	$H_2C(NH_2)\ (COOH)$	20.7%	Amino Acid
L-Histidine		14.1%	Amino Acid
Poly(vinyl acetate)	$[-CH_2CH(OCOCH_3)-]_n$	9.1%	Ester
Cellulose acetate		10.9%	Ester
Sodium alginate		27.7%	Organic Salt
Cellulose sulfate, sodium salt		18.2%	Organic Salt
Poly(4-Vinylpyridine)	$[-CH_2CH(p\text{-}C_5H_4N)-]_n$	21.8%	Aromatic amine
Histamine		13.2%	Amine
Propionamide	$(C_2H_5)CONH_2$	31.8%	Amide
Urea	$(H_2N)_2CO$	17.9%	Urea
1,3-dimethylurea	$(H_3C)HNCONH(CH_3)$	31.7%	Urea
Biuret	$(H_2N)CO(NH)CO(NH_2)$	13.7%	Biuret
Polyacrylamide	$[-CH_2CH(CONH_2)-]_n$	30.1%	Polyamide
Polyvinylpyrrolidone		29.9%	Polyamide
Nylon 6	$[-NH(CH_2)_5CO-]_n$	17.1%	Polyamide
Nylon 6,6 film	$[-NH(CH_2)_6NHCO(CH_2)_4CO-]_n$	16.6%	Polyamide
Polyetherpolyurethane	$[-RHNCOOR'-]_n$	9.5%	Polyurethane
Sodium carbonate	Na_2CO_3	14.3%	Inorganic
Potassium carbonate	K_2CO_3	33.9%	Inorganic
Rubidium carbonate	Rb_2CO_3	37.0%	Inorganic
Calcium hydroxide	$Ca(OH)_2$	23.4%	Inorganic
Sodium bicarbonate	$NaHCO_3$	10.7%	Inorganic
Tetrasodium pyrophosphate	$Na_4P_2O_7$	18.9%	Inorganic

This Sheet Has Been Replaced

The organic complexes formed cover the following range of functional groups that are capable of forming hydrogen bonds with hydrogen peroxide: alcohols, ethers, ketones, acids, amino acids, esters, organic salts, amines, amides, polyamides, polyurethanes, ureas, and biuret. The inorganic complexes include carbonates with sodium, potassium, and rubidium cations, as well as sodium bicarbonate. In addition, the hydrogen peroxide complexes of calcium hydroxide and tetrasodium pyrophosphate were also prepared. The starting materials were finely divided powers or slightly larger crystalline materials, except for nylon 6,6, which was processed as a film with a thickness of 0.12 mm, and polyvinyl methyl ether, which was a 50% by weight aqueous solution.

The hydrogen peroxide complexes obtained with these materials under the test conditions were solids, except for polyvinylpyrrolidone, histamine, poly(vinyl methyl ether), poly(vinyl methyl ketone),propionamide, and 1,3-dimethylurea. The 1,3-dimethylurea and propionamide hydrogen peroxide complexes were free flowing liquids that were easily handled in the vapor phase synthesis process, since no solvent needed to be removed to obtain the final product. The histamine, polyvinylpyrrolidone, poly(vinyl methyl ether), and poly(vinyl methyl ketone) complexes were gummy materials that were not as easy to handle.

Examples 14 and 15 describe additional studies with polyvinylpyrrolidone under different process conditions to obtain the peroxide complex as a free flowing solid product.

Example 14

Hydrogen peroxide complexes with polyvinylpyrrolidone were prepared in which the percent hydrogen peroxide in the polyvinylpyrrolidone complex was varied by changing the ratio of the weight of polyvinylpyrrolidone to the concentration of hydrogen peroxide in the vapor state. The conditions in these tests were identical to those in Example 12, except the weight of polyvinylpyrrolidone was increased from 1.0 gram to 3.0 grams to 5.0 grams. In all tests, the concentration of hydrogen peroxide was held constant at 10.0

This Sheet Has Been Replaced

mg/liter of chamber volume. The results of these tests are presented in Table 15.

Example 15

A hydrogen peroxide complex of PVP was prepared in which the hydrogen peroxide was delivered from a complex of hydrogen peroxide with urea. When hydrogen peroxide is delivered in this manner, it is substantially water free. In this test, 5 grams of PVP was placed in the reaction chamber and 10 mg H_2O_2/liter of chamber volume was delivered into the reaction chamber by heating about 7 grams of a 35% complex of H_2O_2 with urea to a temperature of about 110°C for approximately 5 minutes. The rest of the conditions in this test were the same as those in Example 12. The percentage hydrogen peroxide in the PVP complex and the physical state of the complex are presented in Table 15.

Table 15

EFFECT OF RATIO OF POLYVINYLPYRROLIDONE TO HYDROGEN PEROXIDE IN THE VAPOR STATE ON % HYDROGEN PEROXIDE IN COMPLEX AND PHYSICAL STATE OF PRODUCT

	Weight PVP (g)	Wt% H_2O_2 in Complex	Physical State of Product
Ex. 14	1	29.9	Soft gummy product
	3	23.5	Hard gummy product
	5	17.7	Free flowing solid
Ex. 15	5	19.7	Free flowing solid

The results of these tests demonstrate that a free flowing solid can be obtained with the PVP hydrogen peroxide complex by controlling the ratio of PVP to hydrogen peroxide in the vapor state and, alternatively, by using a substantially water-free hydrogen peroxide vapor source.

INORGANIC HYDROGEN PEROXIDE COMPLEXES

Inorganic hydrogen peroxide complexes are also suitable for use as sterilants as described in detail hereinabove for organic hydrogen peroxide complexes. Peroxide vapor can be released from these inorganic complexes

This Sheet Has Been Replaced

at atmospheric pressure and room temperature. However, as described in greater detail below, substantial amounts of hydrogen peroxide vapor can be released from inorganic peroxide complexes upon rapid heating to a particular release temperature under reduced pressure. In order to successfully release hydrogen peroxide from inorganic peroxide, the heating rate of the inorganic peroxide complexes is preferably at least 5°C/min; more preferably it is at least 10°C per minute; still more preferably at least 50°C/min.; and most preferably, it is at least 1000°C per minute.

A representative listing of these inorganic peroxide complexes, and the weight percent hydrogen peroxide, is presented in Table 16. The titration procedure used to determine the weight percent of H_2O_2 in the complexes was as described in Example 12. Sodium carbonate H_2O_2 complex was purchased from Fluka Chemical Corp. The vapor-phase synthesis procedure used for synthesizing the inorganic peroxide complexes was the same as that disclosed in Example 12, with the exceptions that 10g of the solid inorganic sample instead of 1-5g, and two reaction cycles versus one, were employed.

Example 16

The reaction procedure for liquid-phase synthesis of inorganic hydrogen peroxide complexes was essentially as described by Jones et al. (*J. Chem. Soc., Dalton*, 12:2526-2532, 1980). Briefly, inorganic solids were first dissolved in a 30% aqueous solution of hydrogen peroxide to make a saturated solution, followed by dropwise addition of ethanol. For the potassium oxalate and rubidium carbonate complexes, the white peroxide precipitates were formed as the amount of ethanol added was gradually increased. For potassium carbonate, potassium pyrophosphate and sodium pyrophosphate, the saturated solutions were incubated at -10°C for several hours to facilitate crystalline peroxide complex formation. The complexes were separated from the liquid by vacuum filtration, washed with ethanol at least three times and dried by vacuum.

This Sheet Has Been Replaced

Table 16

COMPOUNDS EVALUATED AND WEIGHT PERCENT HYDROGEN PEROXIDE PRESENT IN COMPLEXES

Chemical Name	Chemical Formula	Wt % H_2O_2 in Complexes[1]		
		Purchased[2]	Vapor[3]	Liquid[3]
Sodium Carbonate	Na_2CO_3	27.35		
Potassium Carbonate	K_2CO_3		7.43	22.70
Robidium Carbonate	Rb_2CO_3		20.31	26.78
Potassium Oxalate	$K_2C_2O_4$		16.13	16.42
Sodium Pyrophosphate	$Na_4P_2O_7$		11.48	23.49
Potassium Pyrophosphate	$K_4P_2O_7$		20.90	32.76
Sodium Orthophosphate	Na_3PO_4		15.67	
Potassium Orthophosphate	K_3PO_4		16.11	

1. The titration procedure employed to determine the weight percent of H_2O_2 in the complexes is the same as the one stated in the previous patent application.
2. Sodium carbonate hydrogen peroxide complex was purchased from Fluka Chemical Corp.
3. The vapor and liquid phase procedures were used for synthesizing the inorganic peroxide.

A differential scanning calorimeter (DSC) (Model PDSC 2920, TA instruments) was used to determine H_2O_2 release or decomposition properties of the inorganic peroxide complexes. The DSC was run at a heating ramp of 10°C/min and at a temperature range of between 30°C and 200°C. under both atmospheric and varying vacuum pressure conditions. Referring now to FIGURE 5, the DSC comprises a sample chamber 110, heating plate 112 and pressure control system. The pressure control system comprises a pressure transducer 114 connected to a pressure gauge 116. The pressure gauge 116 is connected to a controller 118 which is, in turn, connected to a pressure control valve 120. The pressure transducer 114 is in fluid communication with pressure control valve 120 and with pump 122.

This Sheet Has Been Replaced

Potassium oxalate hydrogen peroxide complex synthesized as described hereinabove was placed in a DSC and subjected to a particular vacuum pressure over a temperature range of 50°C to 170°C. As can be seen in FIGURE 6, greater release of H_2O_2, an endothermic process, occurred at lower pressures, while the exothermic decomposition of H_2O_2 was favored at higher pressures. The partial vacuum pressure is preferably less than 20 torr and most preferably less than 10 torr. The actual pressure in the sample chamber is somewhat higher than that measured within the apparatus and the actual temperature of the chamber is somewhat lower than that measured of the metal plate or aluminum platen. Without wishing to be bound by any particular theory of operation, it is believed that the actual pressure used in the sterilization apparatus should be less than the vapor pressure of the inorganic peroxide complex at the actual temperature of the chamber in order to ensure that the complex will release hydrogen peroxide vapor with substantially no decomposition. However, in general, the pressure used is preferably less than 50 torr, more preferably less than 10 torr. In certain embodiments of the invention in which the vapor pressure of the peroxide complex is low, the pressure is preferably less than 5 torr.

In the use of the inorganic peroxide complexes for sterilization, it is critical to complex stability that heating occur rapidly which may be effected by preheating the aluminum plate prior to contacting with the inorganic peroxide composition. In the use of the inorganic peroxide compounds, it is also preferred that the temperature be higher than 86°C.

As discussed above, it is preferred that the inorganic hydrogen peroxide complex be heated rapidly, i.e. as rapidly as 1000°C/minute or more. This can be accomplished by contacting the peroxide with a pre-heated heating plate. A preferred embodiment for accomplishing such rapid heating is shown in FIGURES 7A and 7B. Referring to FIGURE 7A, there is shown an apparatus 125 for injecting peroxide vapor into a sterilization chamber 131 in a closed position. The inorganic hydrogen peroxide complex is incorporated into a peroxide disk 132. The disk 132 comprises five layers: three layers of CSR

This Sheet Has Been Replaced

wrap, peroxide complex powder and aluminum foil coated with polypropylene. The disk 132 is heat sealed around its edge to retain the peroxide complex powder. The peroxide disk 132 is placed underneath a perforated aluminum plate 130 which is attached to housing 150 by aluminum attachment pieces 142. The disk 132 is loosely held in place between O-rings 151. Prior to introduction of peroxide vapor into the chamber, a heated aluminum platen 134 is apart from the peroxide disk 132 and is attached to an aluminum plate 136. A spring (not shown) within the bellow 138 holds the plate 136 down in the closed position. When the chamber 131 is evacuated, the bellow 138 is also evacuated. The plate 136 is seated against O-rings 148, thus separating a peroxide release chamber 152 from passageways 158. The apparatus is held in place and attached to a sterilization chamber 131 by bolts 144, 146, 154 and 156.

Referring to FIGURE 7B, in order to bring the platen 134 up to contact the peroxide disk 132, the bellow 138 is vented. Once the pressure is increased, the bellow 138 moves upward, thereby propeling the heated aluminum platen 134 against the peroxide disk 132. In a preferred embodiment, the aluminum platen 134 is pre-heated to 175°C; however other temperatures can be used. Peroxide vapor is then released from the powder through the CSP layers, passes through the perforations 160 in the perforated aluminum plate 130, and enters the peroxide release chamber 152. The upward movement of the heated aluminum platen 134 also opens the peroxide release chamber 152, allowing peroxide vapor to enter passageways 158 which are in fluid communication with the sterilization chamber.

The inorganic peroxide complexes used in the following two examples to determine amount of peroxide release and sterilization efficacy were potassium pyrophosphate ($K_4P_2O_7 \cdot 3H_2O_2$: PP), potassium oxalate ($K_2C_2O_4 \cdot 1H_2O_2$: PO) and sodium carbonate ($Na_2CO_3 \cdot 1.5\ H_2O_2$: SC).

This Sheet Has Been Replaced

Example 17

Release of Peroxide from SC, PO and PP

The ideal temperature at which H_2O_2 was released from SC, PO and PP was determined by DSC. The actual amount of H_2O_2 released from 2 g of each of these complexes was determined at various temperatures using a 75 liter chamber and the apparatus of FIGURES 7A and 7B. The amount of H_2O_2 released from the PP at 175°C was greater than for SC and PO. Although SC released the least amount of H_2O_2 at 175°C, significantly more release was seen when the amount of sample was increased.

Table 17

RELEASE OF PEROXIDE IN 75 LITER CHAMBER

	SC	PO	PP
Temp. to release H_2O_2 (by DSC)	170°C	150°C	130°C
With 2 grams sample			
At 125°C	0.3 mg/L	0.8 mg/L	1.0 mg/L
At 150°C	1.2 mg/L	2.0 mg/L	1.5 mg/L
At 175°C	1.8 mg/L	2.5 mg/L	3.4 mg/L
With 3 grams sample			
At 175°C	2.3 mg/L		
With 4 grams sample			
At 175°C	2.9 mg/L		

This Sheet Has Been Replaced

Example 18

Efficacy tests using SC, PO and PP

2×10^6 *B. subtilis* var. niger spores were inoculated on a SS blade. Three inoculated blades were first placed in the front, middle and back positions of a Spunguard wrapped 10"x 21"x 3.5" polyphenylene oxide tray. The wrapped tray was then placed in a 75 liter vacuum chamber having an initial vacuum pressure of 0.2 torr. A 5.5" peroxide disk was made by heat-sealing the SC, SO or PP inorganic peroxide powders between three layers of Spunguard and one layer of aluminum foil coated with polypropylene film. The peroxide was released by contacting the disk for 2 minutes with an aluminum plate which had been preheated to 175°C, followed by an additional diffusion time of 8 minutes for a total exposure time of 10 minutes. After treatment, the three blades were separately placed in Trypticase Soy Broth (TSB) at 32°C for 7 days and scored for bacterial growth. The results are summarized in Table 18.

Table 18

EFFICACY TEST RESULTS

Peroxide Complex	Weight of Complex	Peroxide Conc.	Sterility (+/all)
PP	2 grams	3.4 mg/l	0/3
PO	2 grams	2.5 mg/l	0/3
SC	2 grams	1.8 mg/l	1/3
SC	3 grams	2.3 mg/l	0/3
SC	4 grams	2.9 mg/l	0/3

As can be seen in the table, no growth of spores was observed with the exception of 2 g SC (1/3). However, when the amount of SC subjected to vaporization was increased to 3 grams, no bacterial growth was observed. These results underscore the efficacy of sterilization using inorganic hydrogen peroxide compound.

This Sheet Has Been Replaced

Inorganic hydrogen peroxide complexes can be readily incorporated into the sterilization procedures described hereinabove in connection with organic peroxide complexes. For example, inorganic complexes can be used in connection with a plasma sterilization method, or in connection with a self-sterilizing enclosure where peroxide is slowly released from the complex. Similarly, inorganic complexes can also be used in the sterilization of articles having narrow lumens, whereby a vessel containing the inorganic peroxide complex is connected to the lumen. In addition, pressure pulsing of the vapor released from inorganic peroxide complexes can be employed. Other examples of the use of inorganic complexes for sterilization will be apparent to one having ordinary skill in the art upon reference to the present specification.

This Sheet Has Been Replaced

WE CLAIM:

1. An apparatus for hydrogen peroxide sterilization of an article, comprising:

a container for holding the article to be sterilized at a pressure of less than 50 torr; and

a source of hydrogen peroxide vapor in fluid communication with said container, said source comprising an inorganic hydrogen peroxide complex at a temperature greater than 86°C, said source configured so that said vapor can contact said article to effect sterilization.

2. The apparatus of Claim 1, wherein said pressure is less than 20 torr.

3. The apparatus of Claim 1, wherein said pressure is less than 10 torr.

4. The apparatus of Claim 1, wherein said source is located within said container.

5. The apparatus of Claim 1, further comprising an enclosure disposed outside of said container in which said complex is located, and an inlet providing fluid communication betweeen said container and said enclosure, such that vapor released from said complex travels along said inlet and into said container to effect sterilization.

6. The apparatus of Claim 1, wherein said inorganic hydrogen peroxide complex is a complex of sodium carbonate, potassium pyrophosphate or potassium oxalate.

7. The apparatus of Claim 1, further comprising a heater located within said container, whereby said complex is placed on said heater and heated to facilitate the release of said vapor from said complex.

8. The apparatus of Claim 7, wherein said heater is heated prior to contacting with said complex.

9. The apparatus of Claim 1, further comprising a vacuum pump in fluid communication with said container for evacuating the container.

This Sheet Has Been Replaced

* C L M S *

10. The apparatus of Claim 1, further comprising an electrode adapated to generate a plasma around said article.

11. The apparatus of Claim 10, wherein said electrode is inside said container.

12. The apparatus of Claim 10, wherein said electrode is spaced apart from said container and is adapated to flow plasma generated thereby towards and around said article.

13. The apparatus of Claim 1, wherein said complex is in a solid phase.

14. A method for hydrogen peroxide vapor sterilization of an article, comprising:

placing said article into a container; and

contacting the article with a hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex by heating the complex at a rate of at least 5°C/minute to contact and sterilize the article.

15. The method of Claim 14, wherein the heating rate is at least 10°C/minute.

16. The method of Claim 14, wherein the heating rate is at least 50°C/minute.

17. The method of Claim 14, wherein the heating rate is at least 1000°C/minute.

18. The method of Claim 14, wherein the complex has less than 10% water.

19. The method of Claim 14, further comprising heating said complex to facilitate the release of said vapor from said complex.

20. The method of Claim 19, wherein the heating step comprises contacting said complex with a pre-heated heater.

21. The method of Claim 19, wherein said complex is heated to a temperature greater than 86°C.

This Sheet Has Been Replaced

* C L M S *

22. The method of Claim 14, further comprising evacuating the container before introducing said vapor into said container at a pressure of less than 50 torr.

23. The method of Claim 22, wherein said pressure is less than 20 torr.

24. The method of Claim 22, wherein said pressure is less than 10 torr.

25. The method of Claim 14, further comprising generating a plasma around said article after introducing said vapor into said container.

26. The method of Claim 25, wherein said plasma is generated inside the container.

27. The method of Claim 25, wherein said plasma is generated outside the container and flowed inside the container and around said article.

28. The method of Claim 14, wherein the contacting step comprises pressure pulsing of said vapor.

29. A method for hydrogen peroxide sterilization of an article, comprising:

placing the article in a enclosure containing an inorganic hydrogen peroxide complex;

sealing said enclosure; and

allowing said enclosure to stand at a temperature below 70°C for a time sufficient to release hydrogen peroxide vapor from said complex to effect sterilization of the article.

30. The method of Claim 29, wherein said enclosure is allowed to stand at a pressure less than atmospheric pressure.

31. The method of Claim 29, wherein said enclosure is allowed to stand at a temperature below about 40°C.

32. The method of Claim 29, wherein said enclosure is heated to a temperature greater than 23°C to facilitate release of said vapor.

33. The method of Claim 29, wherein said enclosure is selected from the group consisting of a pouch, a container, a chamber and a room.

This Sheet Has Been Replaced

34. The method of Claim 29, wherein said hydrogen peroxide complex is in the form of a powder.

35. The method of Claim 29, wherein said hydrogen peroxide complex is in the form of a tablet.

36. The method of Claim 29, wherein said sealing step comprises sealing said enclosure with a gas permeable material.

37. The method of Claim 36, wherein said gas permeable material is selected from the group consisting of TYVEK™, CSR wrap, and paper.

38. A sealed enclosure containing a sterile product and an inorganic hydrogen peroxide complex capable of releasing hydrogen peroxide vapor.

39. A potassium pyrophosphate hydrogen peroxide complex.

40. A method for hydrogen peroxide vapor sterilization of an article, comprising:

placing said article into a container; and

contacting the article with a hydrogen peroxide vapor to contact and sterilize the article, said vapor being released from an inorganic hydrogen peroxide complex which does not decompose to release a hydrohalic acid.

41. A method for hydrogen peroxide sterilization of an article having an exterior and a narrow lumen therein, comprising:

connecting a vessel containing an inorganic peroxide complex to the lumen of the article;

placing the article within a container, whereby said vessel remains connected to the lumen;

reducing the pressure within said container; and

contacting the lumen of the article with hydrogen peroxide vapor released from said inorganic peroxide complex at a temperature less than 70°C.

This Sheet Has Been Replaced

VAPOR STERILIZATION USING INORGANIC HYDROGEN PEROXIDE COMPLEXES

Abstract of the Disclosure

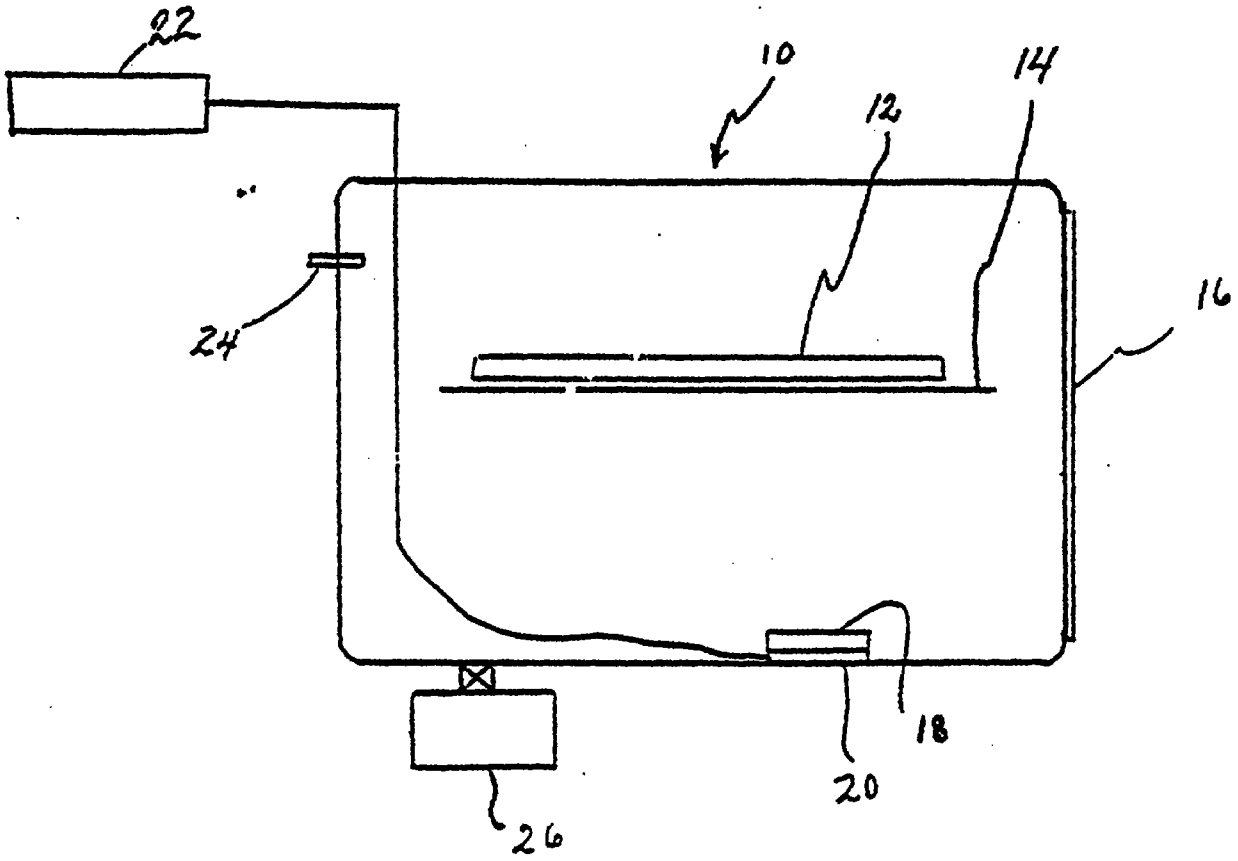
An apparatus and process for hydrogen peroxide vapor sterilization of medical instruments and similar devices make use of hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex. The peroxide vapor can be released at room temperature and atmospheric pressure; however, the pressure used can be less than 50 torr and the temperature greater than 86°C to facilitate the release of hydrogen peroxide vapor. The heating rate can be greater than 5°C. Optionally, a plasma can be used in conjunction with the vapor.

DEA-8122
102795

[NSB]

This Sheet Has Been Replaced

FIG. 1



This Sheet Has Been Replaced

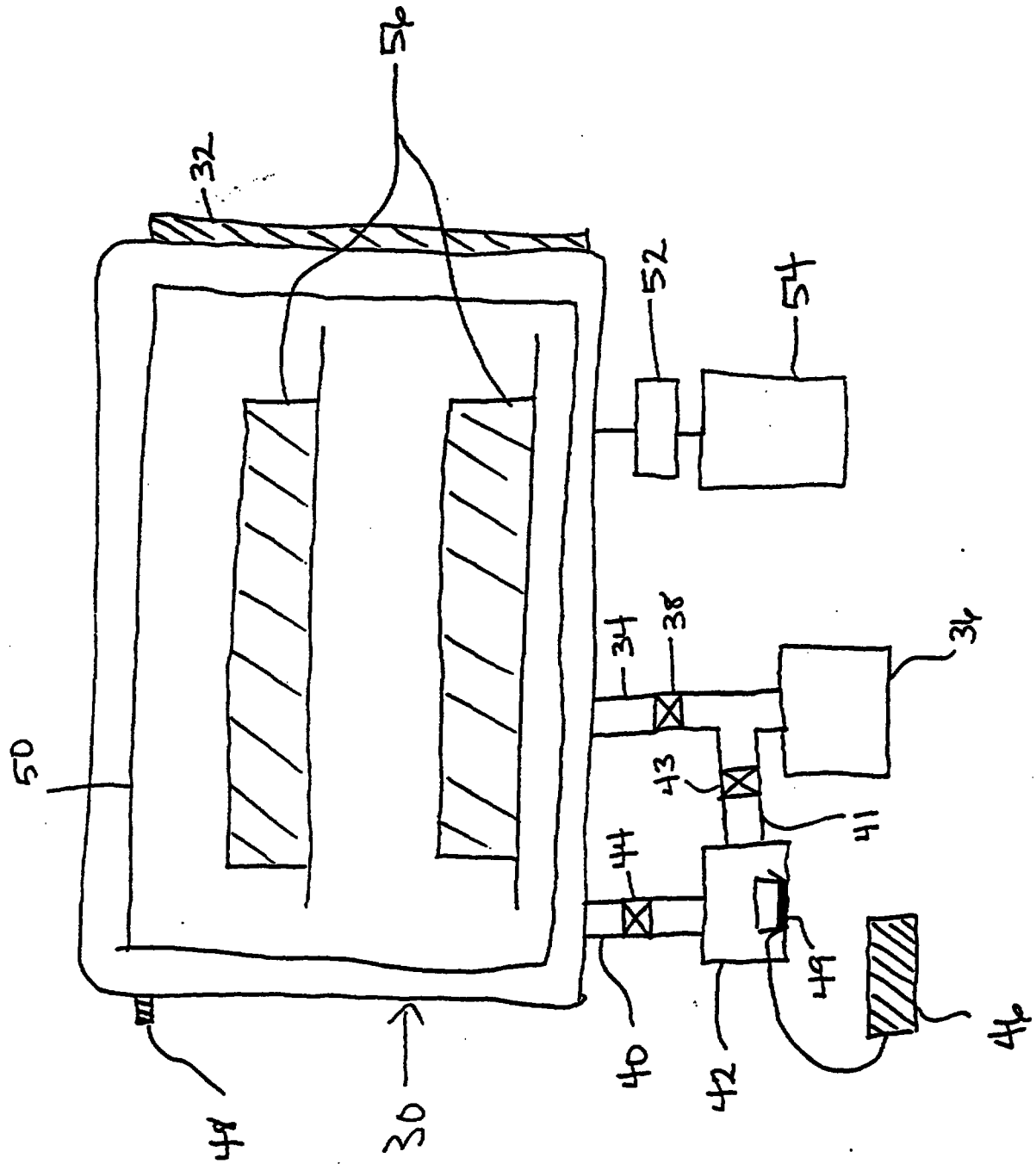


FIGURE 2

This Sheet Has Been Replaced

FIG. 3A

This Sheet Has Been Replaced

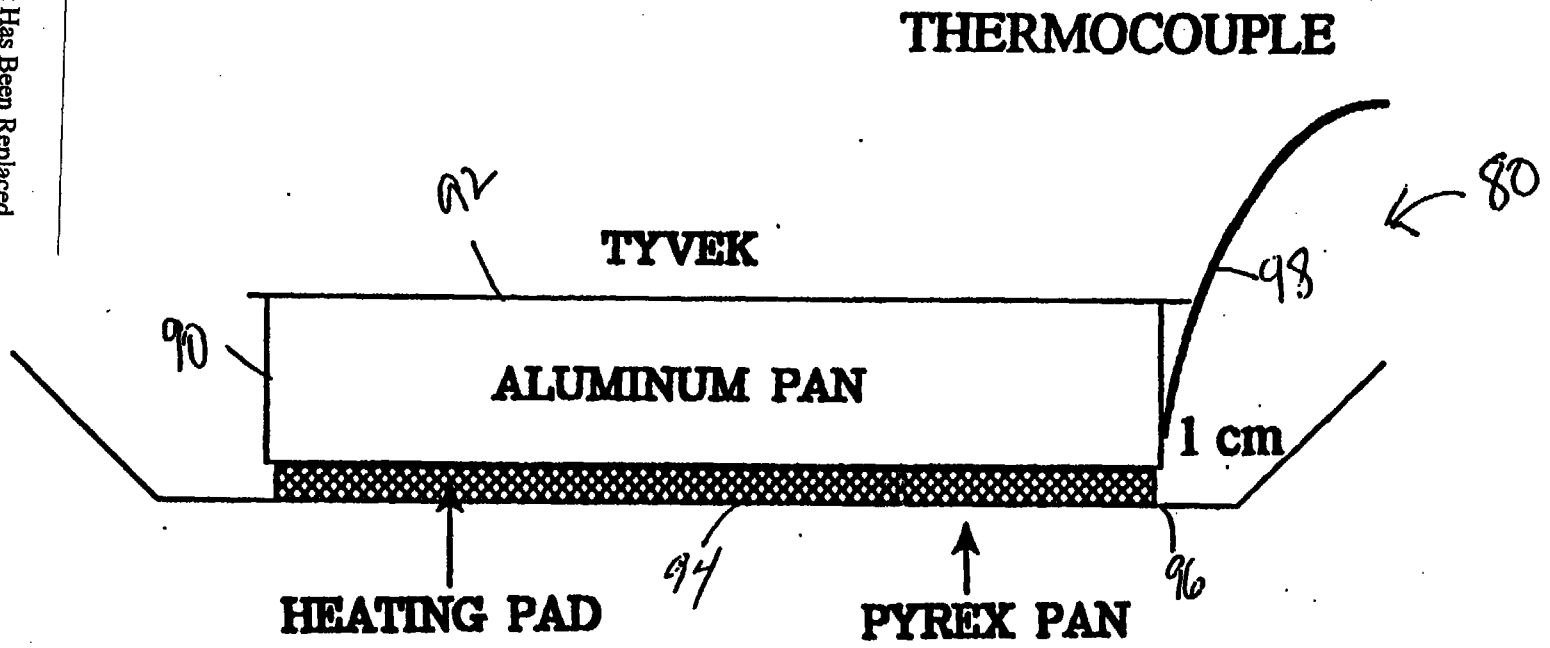


FIG. 3B

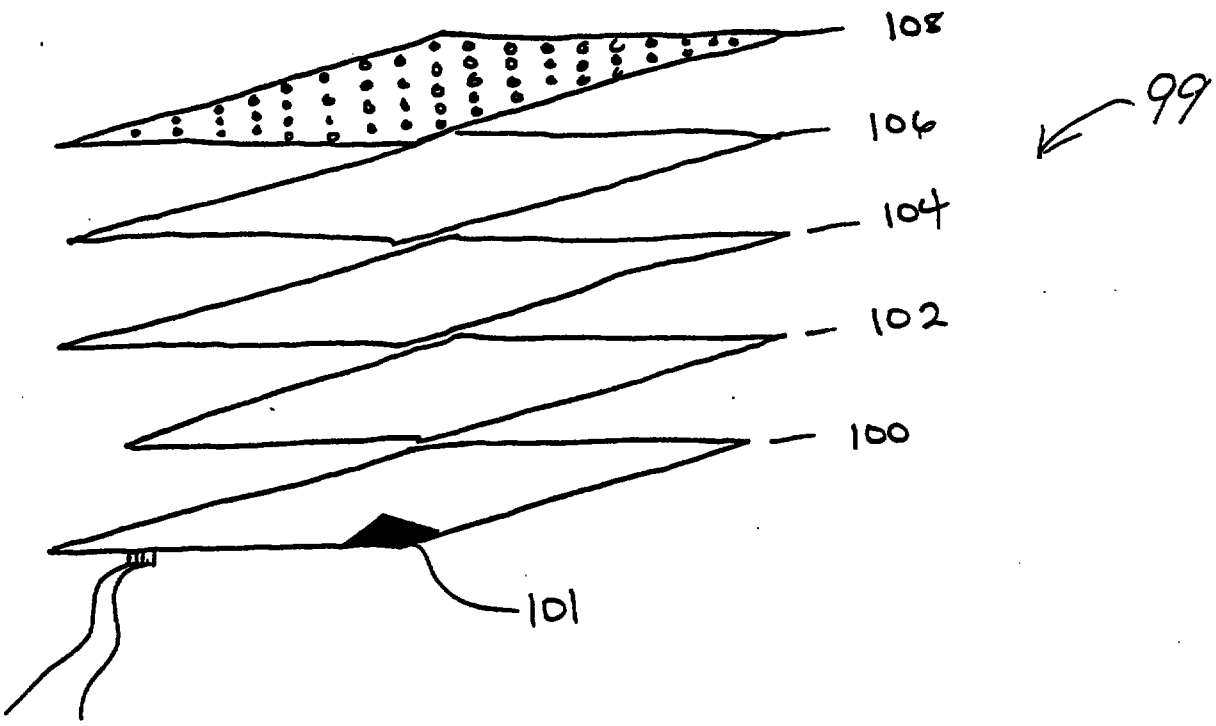
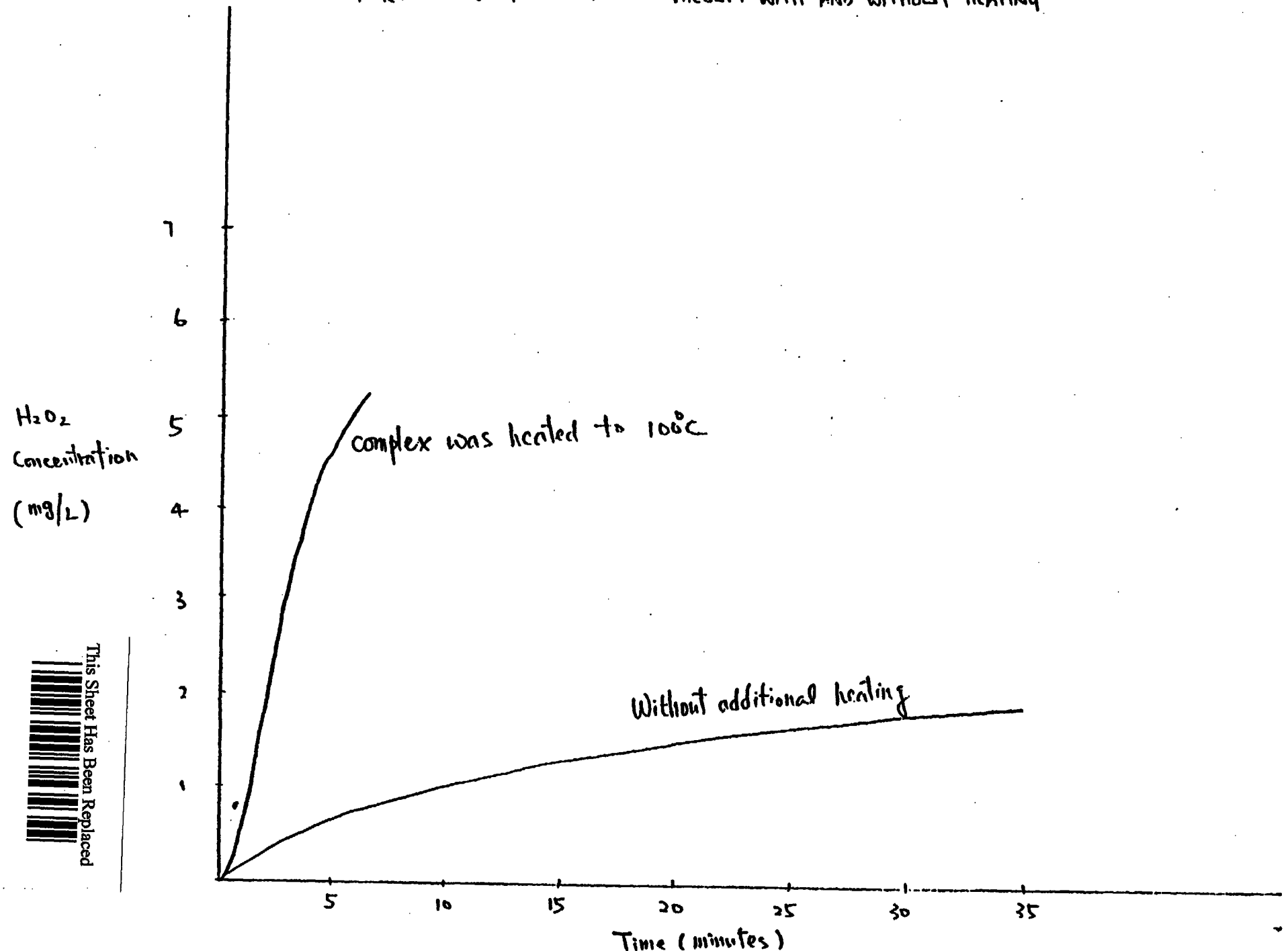


FIGURE 3B

This Sheet Has Been Replaced

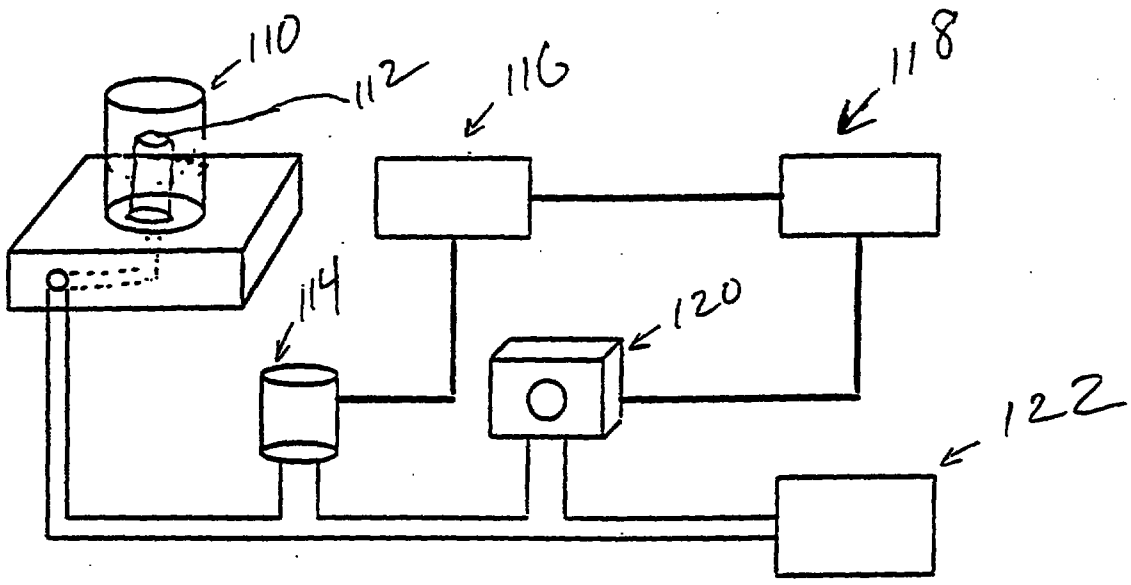
THE RELEASE OF HYDROGEN PEROXIDE FROM GLYCINE ANHYDRIDE PEROXIDE COMPLEX UNDER VACUUM WITH AND WITHOUT HEATING



This Sheet Has Been Replaced

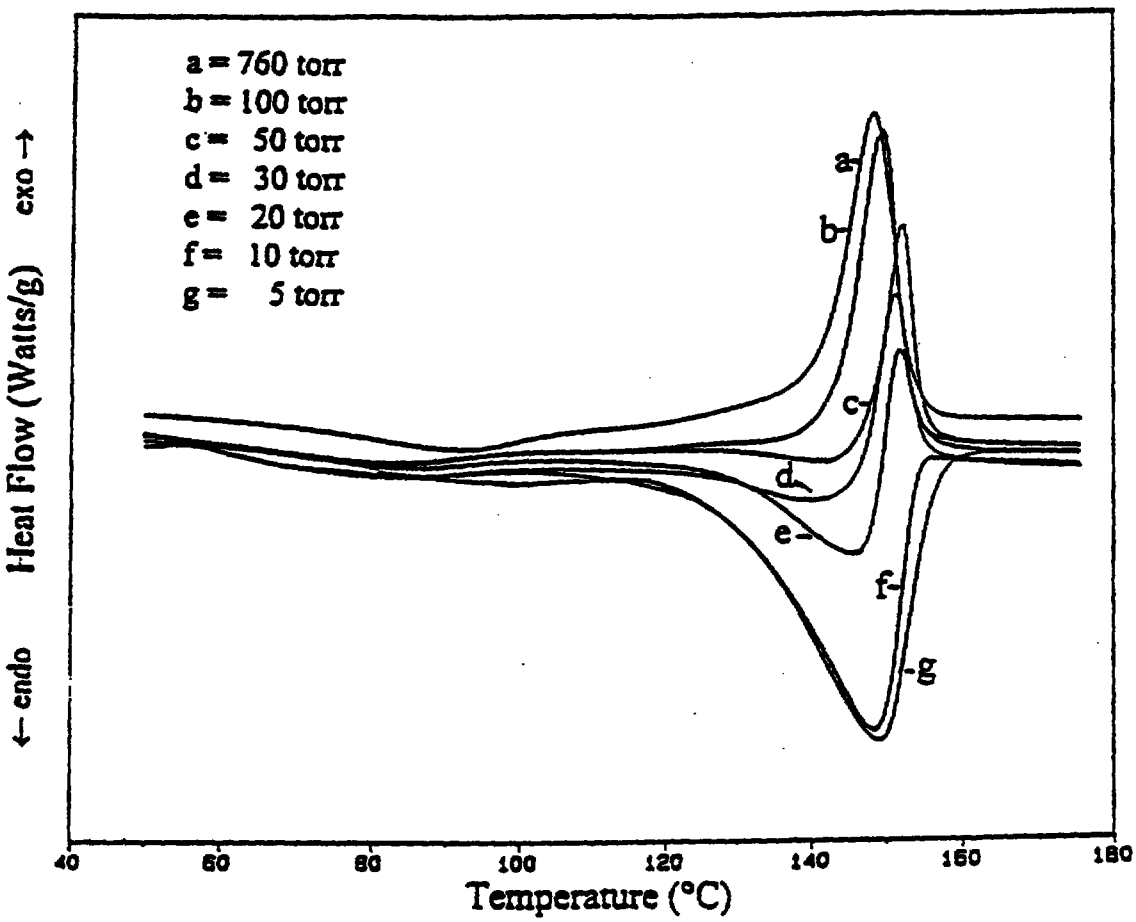
FIG. 5

9610966-5
SD



This Sheet Has Been Replaced

FIG. 6



This Sheet Has Been Replaced

This Sheet Has Been Replaced

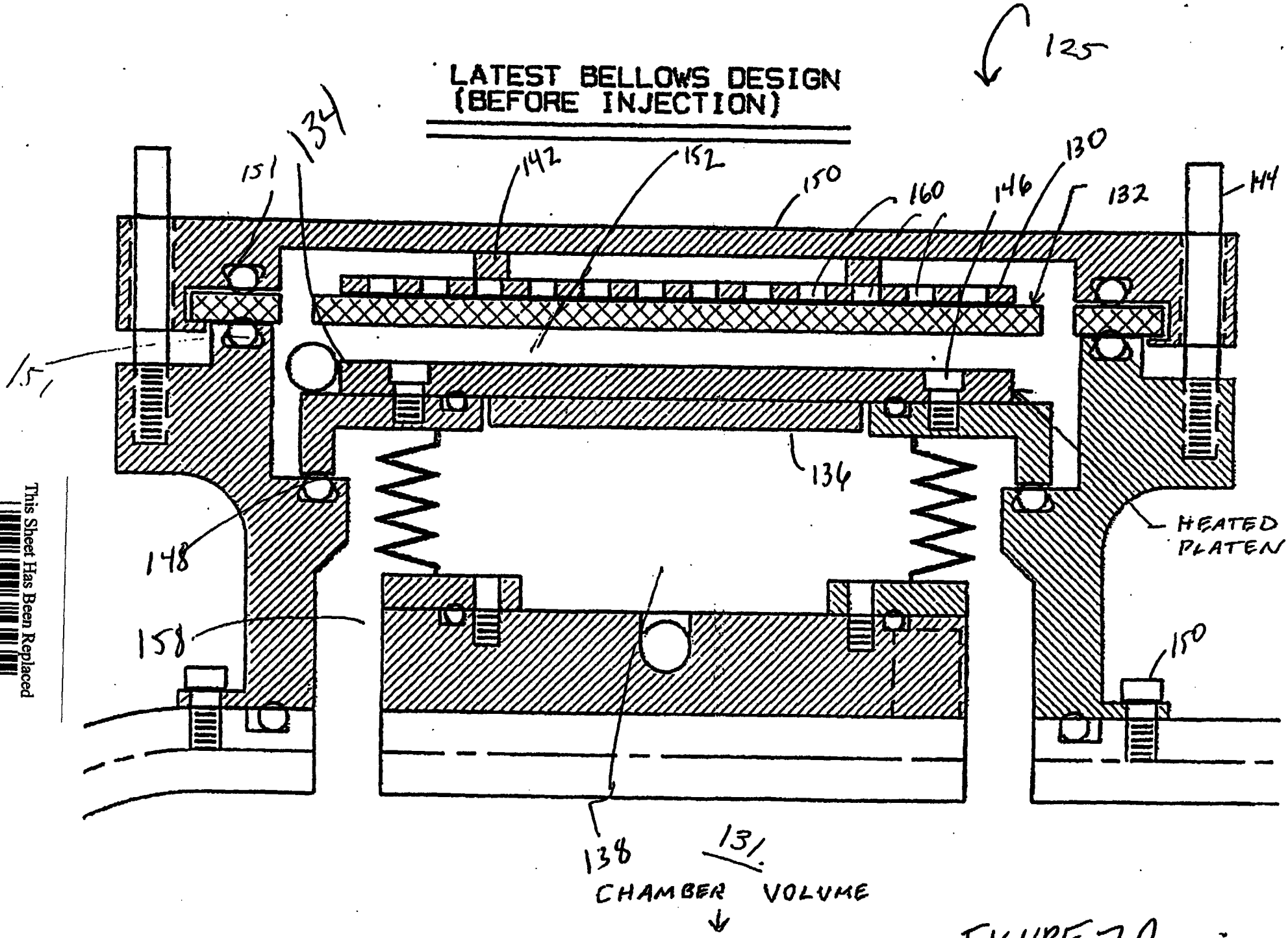
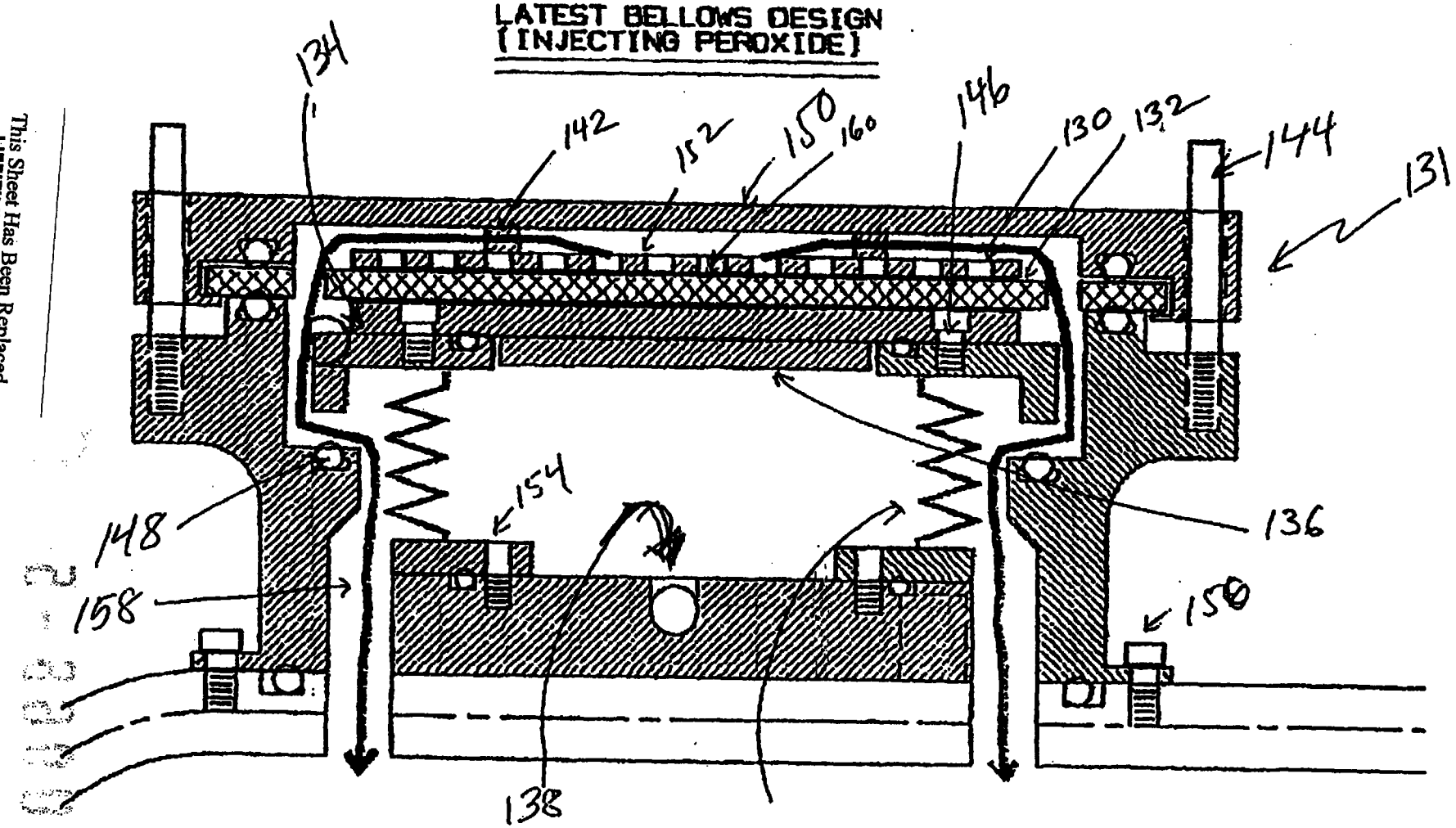


FIGURE 7A

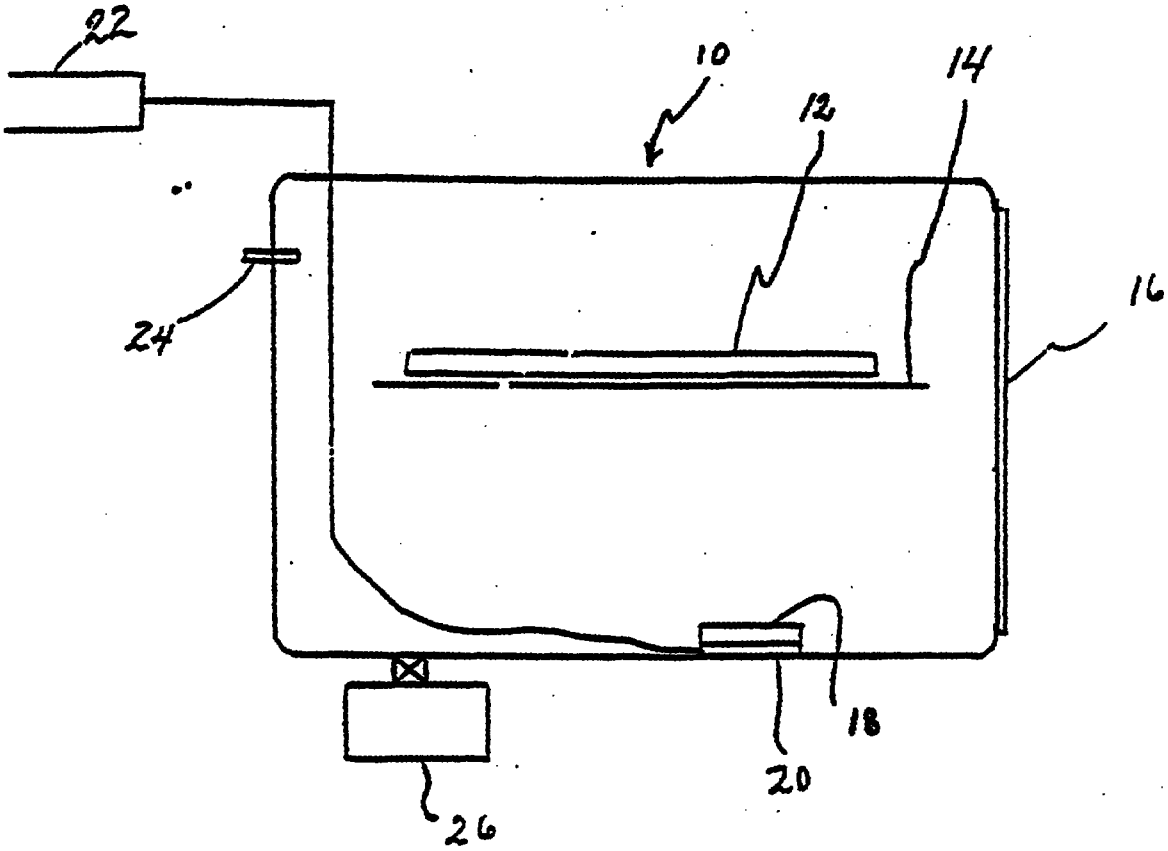
FIG. 7B



This Sheet Has Been Replaced

FIGURE 7B

FIG. 1



REPLACEMENT SHEETS SG
☐ Description : paged ..... to paged .....
☐ Claim(s) : paged ..... to paged .....
☑ Drawing(s) : paged 11 to paged 11
☐ Abstract : paged ..... to paged .....

DATE OF RECEIPT 11/12/96

REPLACEMENT SHEET
11 DEC 1996

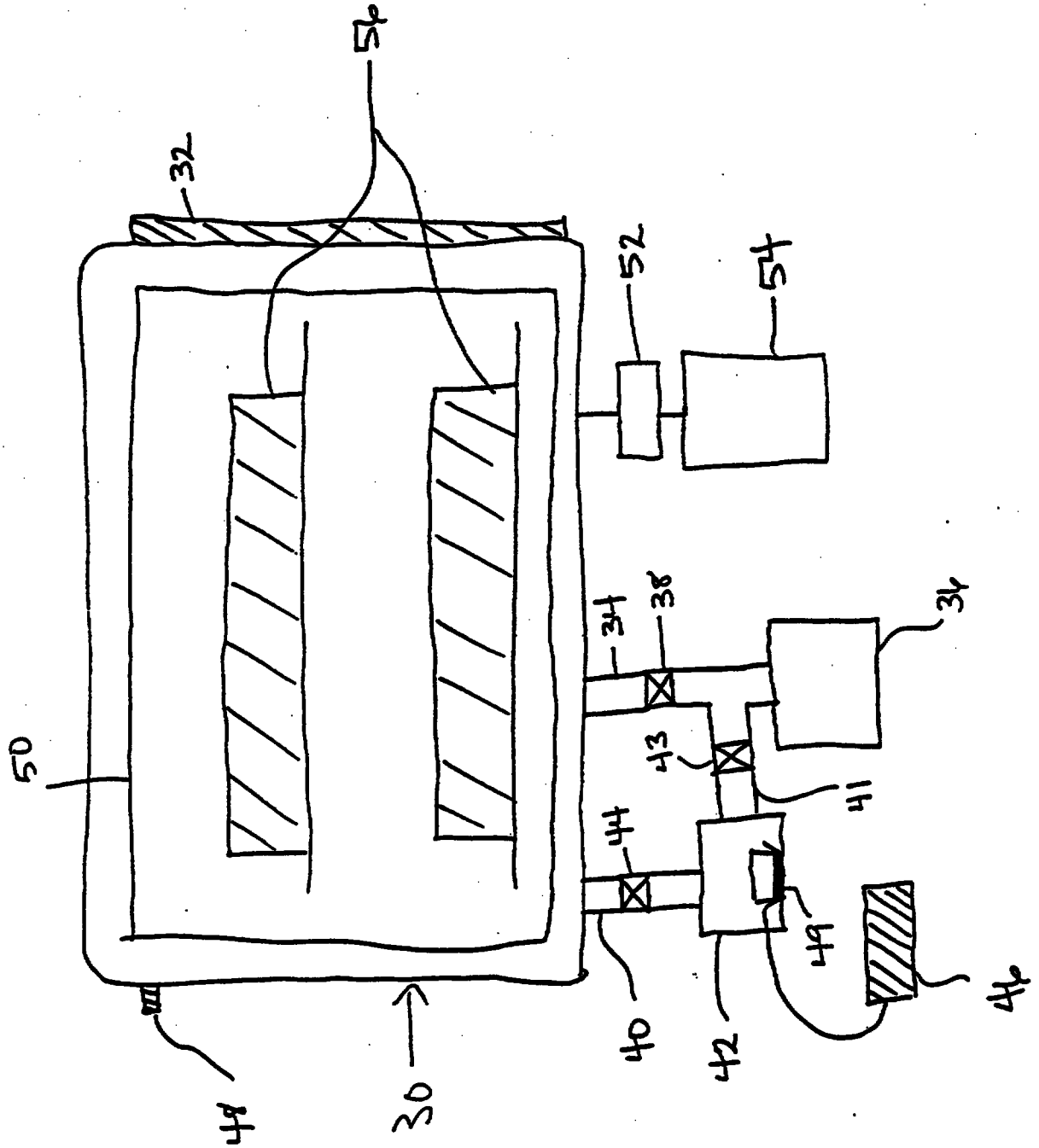


FIGURE 2

REPLACEMENT SHEET
11 DEC 1996

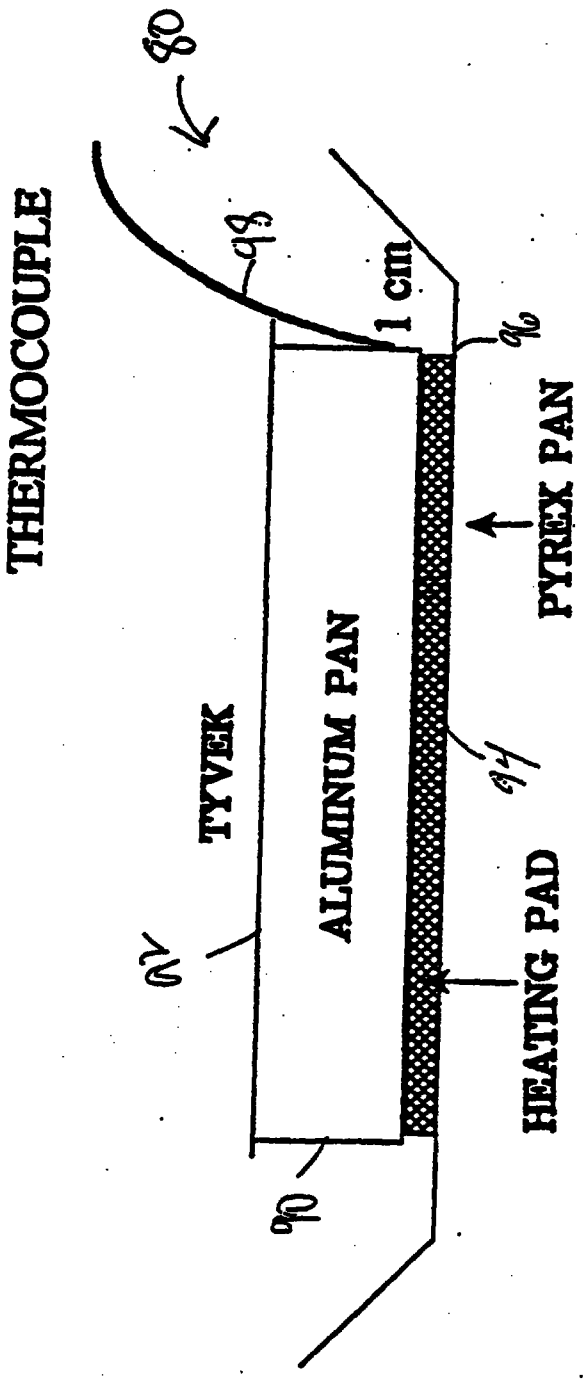


FIG. 3A

REPLACEMENT SHEET
11 DEC 1996

FIG. 3B

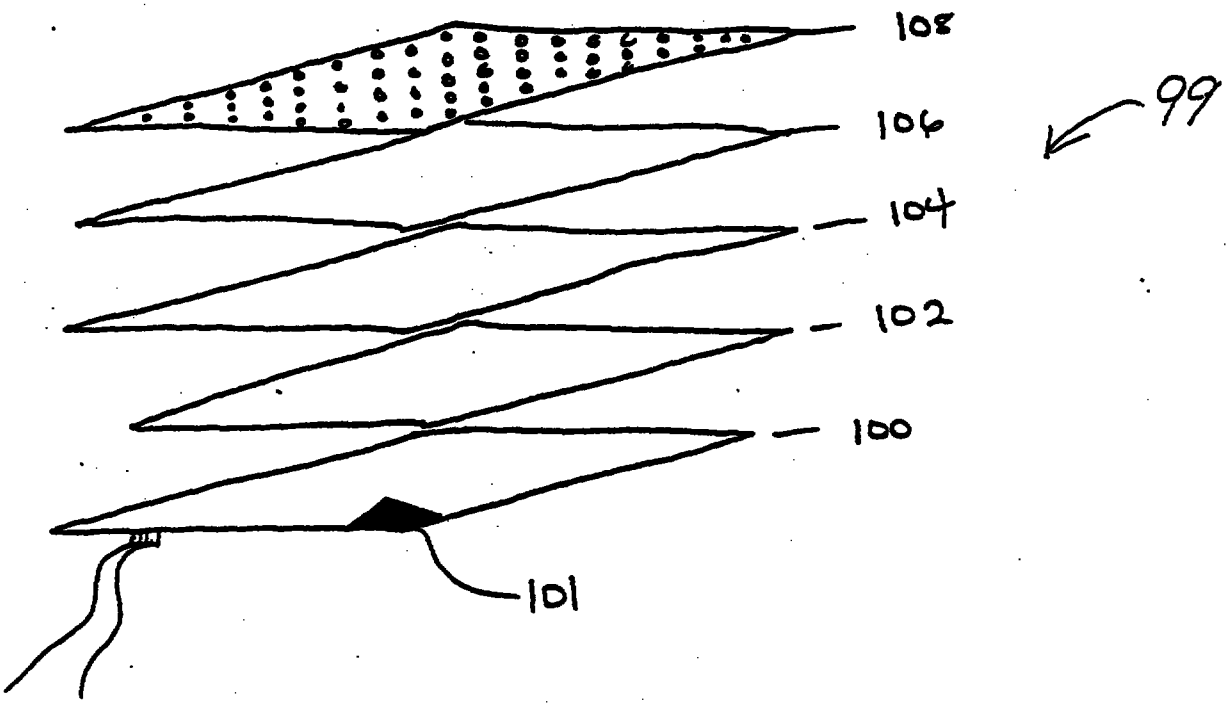


FIGURE 3B

REPLACEMENT SHEET
11 DEC 1996

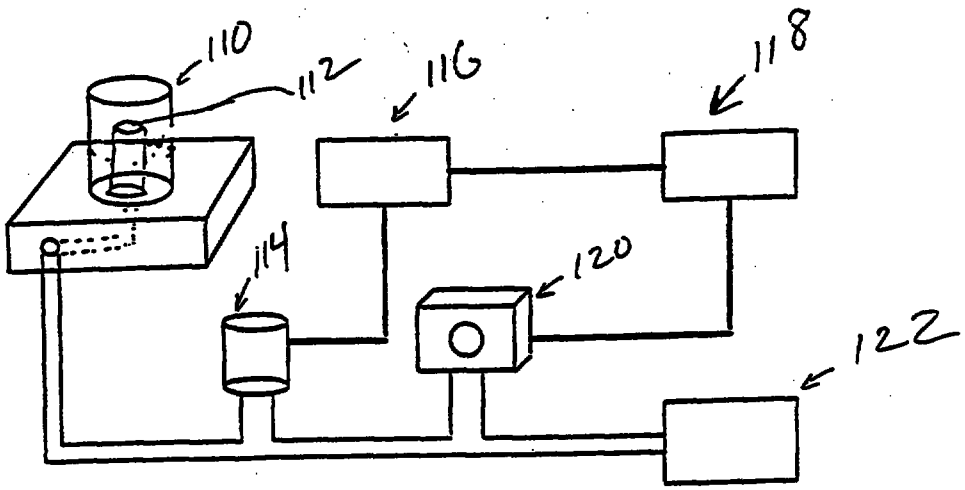
THIS SHEET HAS BEEN REPLACED

THE RELEASE OF HYDROGEN PEROXIDE FROM GLYCINE ANHYDRIDE PEROXIDE COMPLEX UNDER VACUUM WITH AND WITHOUT HEATING

REPLACEMENT SHEET
11 DEC 1996

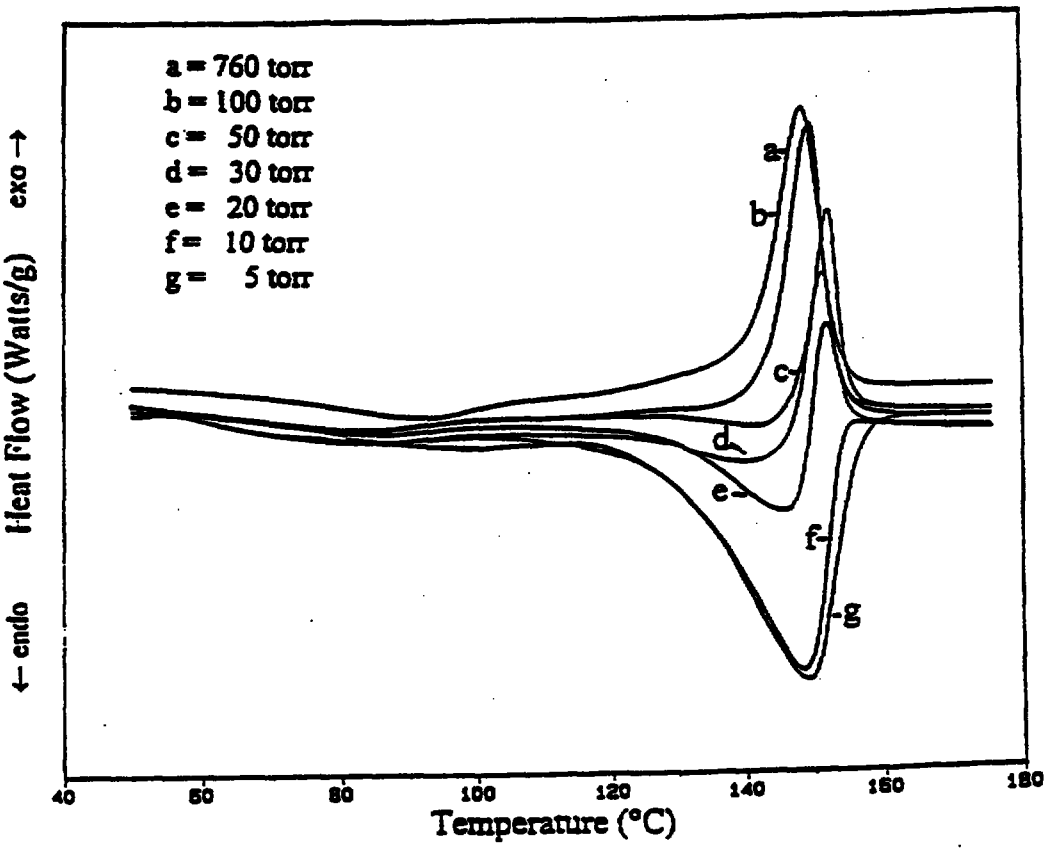
This Sheet Has Been Replaced

FIG. 5



REPLACEMENT SHEET
11 DEC 1996

FIG. 6



REPLACEMENT SHEET
11 DEC 1996

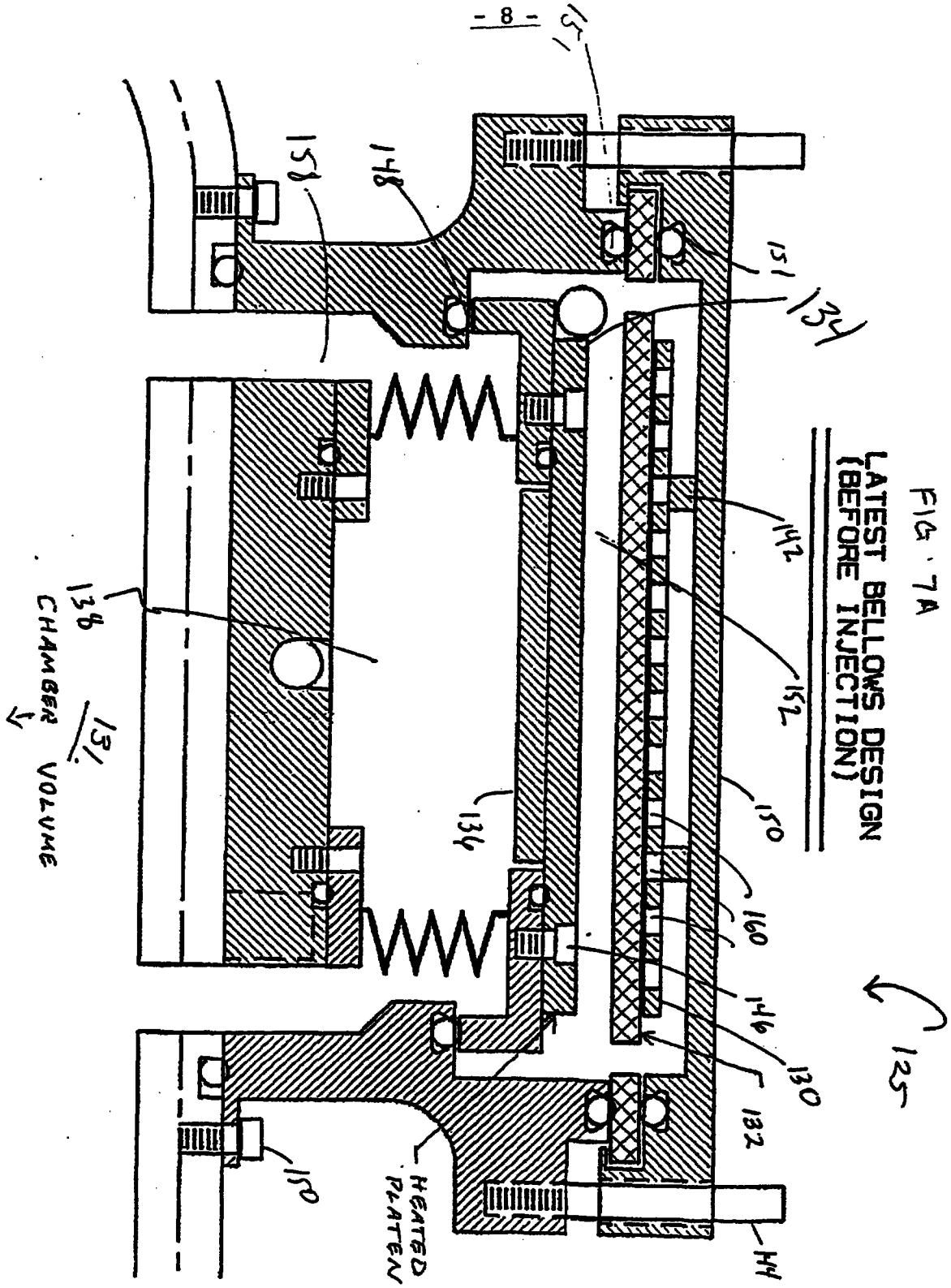


FIG. 7A

REPLACEMENT SHEET
11 DEC 1996

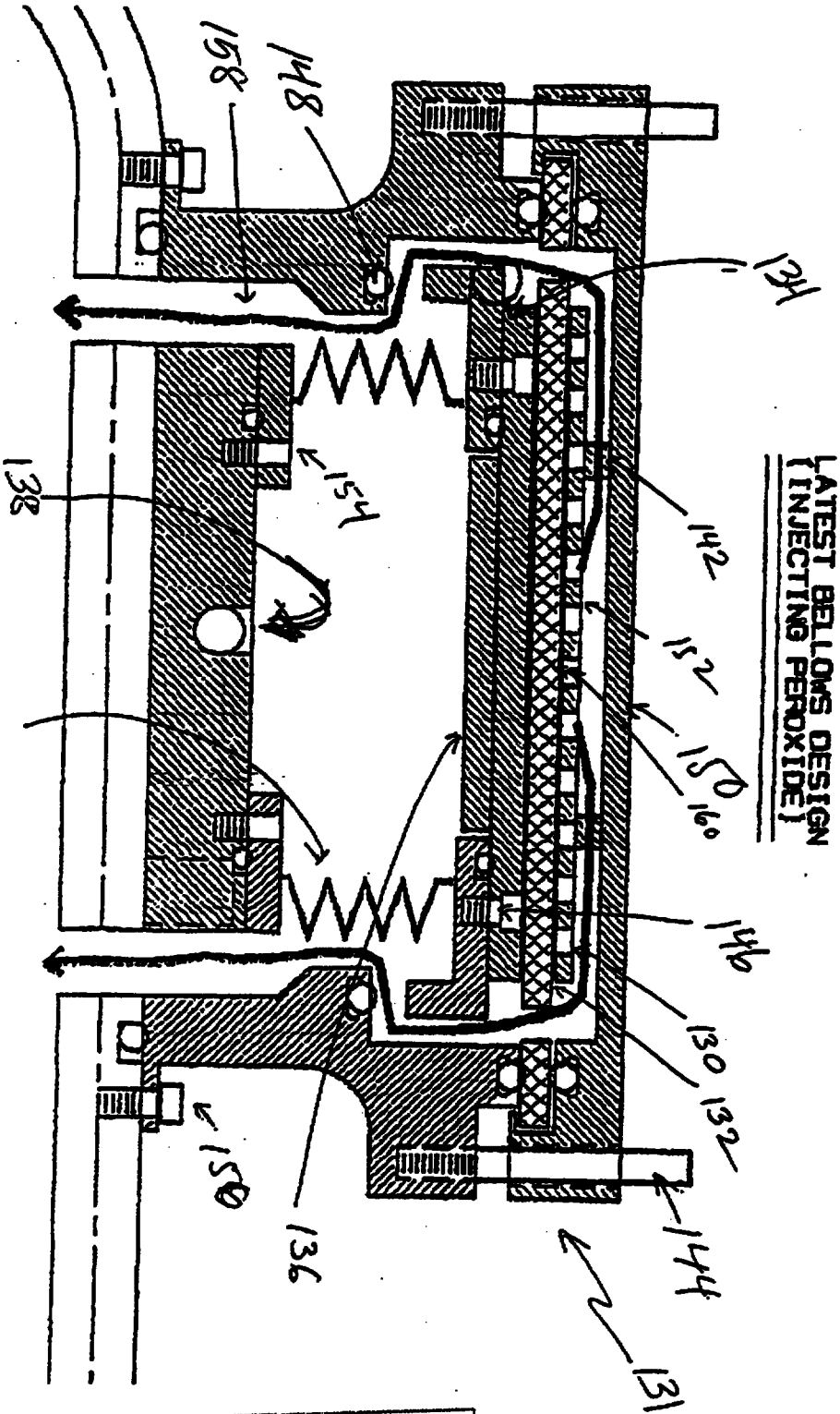


FIG. 7B

REPLACEMENT SHEET
11 DEC 1996

PCT/US96-5 IPEA

VAPOR STERILIZATION USING INORGANIC HYDROGEN PEROXIDE COMPLEXES

Related Applications

This application is a continuation-in-part of U.S. patent application Serial No. 08/369,786, filed January 6, 1995, which is a continuation-in-part of Serial No. 08/234,738, filed April 28, 1994.

Background of the Invention

Field of the Invention

This invention relates to an apparatus and process for using hydrogen peroxide vapor to sterilize articles such as medical instruments, and more particularly to the use of an inorganic hydrogen peroxide complex for such a process.

Description of the Related Art

Medical instruments have traditionally been sterilized using either heat, such as is provided by steam, or a chemical, such as formaldehyde or ethylene oxide in the gas or vapor state. Each of these methods has drawbacks. Many medical devices, such as fiber optic devices, endoscopes, power tools, etc. are sensitive to heat, moisture, or both. Formaldehyde and ethylene oxide are both toxic gases that pose a potential hazard to healthcare workers. Problems with ethylene oxide are particularly severe, because its use requires long aeration times to remove the gas from articles that have been sterilized. This makes the sterilization cycle time undesirably long. In addition, both formaldehyde and ethylene oxide require the presence of a substantial amount of moisture in the system. Thus, devices to be sterilized must be humidified before the chemical is introduced or the chemical and moisture must be introduced simultaneously. Moisture plays a role in sterilization with a variety of other chemicals in the gas

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEETS SG
☑ Description : paged 1 to paged 50
☑ Claim(s) : paged 51 to paged 54
☑ Drawing(s) : paged 55 to paged ---
☑ Abstract : paged 55 to paged ---
DATE OF RECEIPT 14/11

or vapor state, in addition to ethylene oxide and formaldehyde, as shown in Table 1.

Table 1

Chemical	Relative Humidity Requirements for Optimal Efficacy	Literature Reference
Ethylene oxide	25-50%	1
Propylene oxide	25-50%	1
Ozone	75-90%	2
Formaldehyde	>75%	1
Glutaraldehyde	80-90%	3
Chlorine dioxide	60-80%	4
Methyl bromide	40-70%	1
β-Propiolactone	>75%	1
Peracetic acid	40-80%	5

1. Bruch, C. W. Gaseous Sterilization, *Ann. Rev. Microbiology* 15:245-262 (1961).
2. Janssen, D. W. and Schneider, P.M. Overview of Ethylene Oxide Alternative Sterilization Technologies, *Zentralsterilisation* 1:16-32 (1993).
3. Bovallius, A. and Anas, P. Surface-Decontaminating Action of Glutaraldehyde in the Gas-Aerosol Phase. Applied and Environmental Microbiology, 129-134 (Aug. 1977).
4. Knapp, J. E. et al. Chlorine Dioxide As a Gaseous Sterilant, Medical Device & Diagnostic Industry, 48-51 (Sept. 1986).
5. Portner, D.M. and Hoffman, R.K. Sporicidal Effect of Peracetic Acid Vapor, *Applied Microbiology* 16:1782-1785 (1968).

Sterilization using hydrogen peroxide vapor has been shown to have some advantages over other chemical sterilization processes (see, e.g., U.S. Pat. Nos. 4,169,123 and 4,169,124), and the combination of hydrogen peroxide with a plasma provides additional advantages, as disclosed in U.S. Pat. 4,643,876. In these disclosures the hydrogen peroxide vapor is generated from an aqueous solution of hydrogen peroxide, which ensures that there is moisture present in the system. These disclosures, together with those summarized in Table 1, teach that moisture is required for hydrogen peroxide in the vapor phase to be effective or to exhibit its maximum sporicidal activity. However, the

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

use of aqueous solutions of hydrogen peroxide to generate hydrogen peroxide vapor for sterilization may cause problems. At higher pressures, such as atmospheric pressure, excess water in the system can cause condensation. Thus, one must reduce the relative humidity in a sterilization enclosure before introducing the aqueous hydrogen peroxide vapor.

The sterilization of articles containing diffusion-restricted areas, such as long narrow lumens, presents a special challenge for hydrogen peroxide vapor that has been generated from an aqueous solution of hydrogen peroxide, because:

1. Water has a higher vapor pressure than hydrogen peroxide and will vaporize faster than hydrogen peroxide from an aqueous solution.

2. Water has a lower molecular weight than hydrogen peroxide and will diffuse faster than hydrogen peroxide in the vapor state.

Because of this, when an aqueous solution of hydrogen peroxide is vaporized, the water reaches the items to be sterilized first and in higher concentration. The water vapor therefore becomes a barrier to the penetration of hydrogen peroxide vapor into diffusion restricted areas, such as small crevices and long narrow lumens. One cannot solve the problem by removing water from the aqueous solution and using more concentrated hydrogen peroxide, since concentrated solutions of hydrogen peroxide, i.e., greater than 65% by weight, can be hazardous, due to the oxidizing nature of the solution.

U.S. Patents 4,642,165 and 4,744,951 attempt to solve this problem. The former discloses metering small increments of a hydrogen peroxide solution onto a heated surface to ensure that each increment is vaporized before the next increment is added. Although this helps to eliminate the difference in the vapor pressure and volatility between hydrogen peroxide and water, it does not address the fact that water diffuses faster than hydrogen peroxide in the vapor state.

The latter patent describes a process for concentrating hydrogen peroxide from a relatively dilute solution of hydrogen peroxide and water and supplying the concentrated hydrogen peroxide in vapor form to a sterilization

REPLACEMENT SHEET
08 APR 1997

chamber. The process involves vaporizing a major portion of the water from the solution and removing the water vapor produced before injecting the concentrated hydrogen peroxide vapor into the sterilization chamber. The preferred range for the concentrated hydrogen peroxide solution is 50% to 80% by weight. This process has the disadvantage of working with solutions that are in the hazardous range; i.e., greater than 65% hydrogen peroxide, and also does not remove all of the water from the vapor state. Since water is still present in the solution, it will vaporize first, diffuse faster, and reach the items to be sterilized first. This effect will be especially pronounced in long narrow lumens.

U.S. Pat. 4,943,414 discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. This system has the advantage that the water and hydrogen peroxide vapor are pulled through the lumen by the pressure differential that exists, increasing the sterilization rate for lumens, but it has the disadvantage that the vessel needs to be attached to each lumen to be sterilized. In addition, water is vaporized faster and precedes the hydrogen peroxide vapor into the lumen.

U.S. Pat. No. 5,008,106 discloses that a substantially anhydrous complex of PVP and H_2O_2 is useful for reducing the microbial content of surfaces. The complex, in the form of a fine white powder, is used to form antimicrobial solutions, gels, ointments, etc. It can also be applied to gauze, cotton swabs, sponges and the like. The H_2O_2 is released upon contact with water present on the surfaces containing the microbes. Thus, this method too requires the presence of moisture to effect sterilization.

Certain inorganic hydrogen peroxide complexes have been reported including examples within the following classes: alkali metal and ammonium carbonates, alkali metal oxalates, alkali metal phosphates, alkali metal pyrophosphates, fluorides and hydroxides. U.S.S.R. patent document No. SU 1681860 (Nikolskaya et al.) discloses that surfaces can be decontaminated,

REPLACEMENT SHEET
08 APR 1997

although not necessarily sterilized, using ammonium fluoride peroxohydrate ($NH_4F \cdot H_2O_2$). However, this inorganic peroxide complex provides decontamination only within the very narrow temperature range of 70-86°C. Even within this range, decontamination times were quite long, requiring at least two hours. Additionally, it is known that ammonium fluoride decomposes to ammonia and hydrofluoric acid at temperatures above 40°C. Due to its toxicity and reactivity, hydrofluoric acid is undesirable in most sterilization systems. Moreover, Nikolskaya et al. disclose that despite the release of 90% of its hydrogen peroxide at 60°C, $NH_4F \cdot H_2O_2$ is ineffective at decontamination of surfaces at this temperature. Thus, it appears that a factor other than hydrogen peroxide is responsible for the decontamination noted.

Hydrogen peroxide is capable of forming complexes with both organic and inorganic compounds. The binding in these complexes is attributed to hydrogen bonding between electron rich functional groups in the complexing compound and the peroxide hydrogen. The complexes have been used in commercial and industrial applications such as bleaching agents, disinfectants, sterilizing agents, oxidizing reagents in organic synthesis, and catalysts for free-radical-induced polymerization reactions.

Generally, these types of compounds have been prepared by the crystallization of the complex from an aqueous solution. For example, urea hydrogen peroxide complex was prepared by Lu et al. (*J. Am. Chem. Soc.* 63(1):1507-1513 (1941)) in the liquid phase by adding a solution of urea to a solution of hydrogen peroxide and allowing the complex to crystallize under the proper conditions. U.S. Pat. No. 2,986,448 describes the preparation of sodium carbonate hydrogen peroxide complex by treating a saturated aqueous solution of Na_2CO_3 with a solution of 50 to 90% H_2O_2 in a closed cyclic system at 0 to 5°C for 4 to 12 hours. More recently, U.S. Pat. No. 3,870,783 discloses the preparation of sodium carbonate hydrogen peroxide complex by reacting aqueous solutions of hydrogen peroxide and sodium carbonate in a batch or continuous crystallizer. The crystals are separated by filtration or centrifugation and the liquors used to produce more sodium carbonate solution. Titova et al.

REPLACEMENT SHEET
08 APR 1997

(*Zhurnal Neorg. Khim.*, 30:2222-2227, 1985) describe the synthesis of potassium carbonate peroxyhydrate ($K_2CO_3 \cdot 3H_2O_2$) by reaction of solid potassium carbonate with an aqueous solution of hydrogen peroxide at low temperature followed by crystallization of the complex from ethanol. These methods work well for peroxide complexes that form stable, crystalline free-flowing products from aqueous solution.

U.S. Pat. Nos. 3,376,110 and 3,480,557 disclose the preparation of a complex of hydrogen peroxide with a polymeric N-vinylheterocyclic compound (PVP) from aqueous solution. The resultant complexes contained variable amounts of hydrogen peroxide and substantial amounts of water. U.S. Pat. No. 5,008,093 teaches that free-flowing, stable, substantially anhydrous complexes of PVP and H_2O_2 could be obtained by reacting a suspension of PVP and a solution of H_2O_2 in an anhydrous organic solvent like ethyl acetate. More recently, U.S. Pat. No. 5,077,047 describes a commercial process for producing the PVP-hydrogen peroxide product by adding finely divided droplets of a 30% to 80% by weight aqueous solution of hydrogen peroxide to a fluidized bed of PVP maintained at a temperature of ambient to 60°C. The resultant product was found to be a stable, substantially anhydrous, free flowing powder with a hydrogen peroxide concentration of 15 to 24%.

U.S. Pat. No. 5,030,380 describes the preparation of a solid polymeric electrolytic complex with hydrogen peroxide by first forming a complex in aqueous solution and then drying the reaction product under vacuum or by spray drying at a low enough temperature to avoid thermal degradation of the product.

All of these previous methods of preparing hydrogen peroxide complexes use solutions of hydrogen peroxide. Either the complex is formed in a solution containing hydrogen peroxide or droplets of a hydrogen peroxide solution are sprayed onto a fluidized bed of the reactant material.

Vapor phase and gas phase reactions are well known synthesis methods. For example, U.S. Pat. No. 2,812,244 discloses a solid-gas process for dehydrogenation, thermal cracking, and demethanation. Fujimoto et al. (*J.*

REPLACEMENT SHEET
08 APR 1997

Catalysis, 133:370-382 (1992)) described a vapor-phase carboxylation of methanol. Zellers et al. (*Anal. Chem.*, 62:1222-1227 (1990)) discussed the reaction of styrene vapor with a square-plannar organoplatinum complex. These prior art vapor- and gas-phase reactions, however, were not used to form hydrogen peroxide complexes.

Summary of the Invention

One aspect of the present invention relates to an apparatus for hydrogen peroxide sterilization of an article. This apparatus includes a container for holding the article to be sterilized at a pressure of less than 50 torr. Preferably, the pressure is less than 20 torr, and more preferably less than 10 torr. The apparatus also includes a source of hydrogen peroxide vapor in fluid communication with the container. The source includes an inorganic hydrogen peroxide complex at a temperature greater than 86°C, and is configured so that the peroxide vapor can contact the article to effect sterilization. The source can be located within the container, or alternatively, the apparatus can include an enclosure disposed outside of the container in which the complex is located, and an inlet providing fluid communication betweeen the container and the enclosure, such that vapor released from the complex travels along the inlet and into the container to effect sterilization. The inorganic hydrogen peroxide complex can be a complex of sodium carbonate, potassium pyrophosphate or potassium oxalate. Preferably, the apparatus, also includes a heater located within the container, whereby the complex is placed on the heater and heated to facilitate the release of the vapor from the complex. Such a heater can be heated prior to contacting with the complex. The apparatus can also include a vacuum pump in fluid communication with the container for evacuating the container. In some embodiments, the apparatus includes an electrode adapated to generate a plasma around the article. Such an electrode can be inside the container, or can be spaced apart from the container and adapated to flow plasma generated thereby towards and around the article. In a preferred embodiment, the complex is in a solid phase.

REPLACEMENT SHEET
08 APR 1997

Another aspect of the present invention relates to a method for hydrogen peroxide vapor sterilization of an article. This method includes placing the article into a container, and contacting the article with a hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex by heating the complex at a rate of at least 5°C/minute to contact and sterilize the article. Preferably, the heating rate is at least 10°C/minute, more preferably, at least 50°C/minute, and still more preferably at least 1000°C/minute. The complex preferably has less than 10% water. The complex can be heated, preferably to a temperature greater than 86°C to facilitate the release of the vapor from the complex. The container can be evacuated before introducing the vapor into the container at a pressure of less than 50 torr, more preferably less than 20 torr, and still more preferably less than 10 torr. Optionally, a plasma can be generated around the article after introducing the vapor into the container. The plasma can be generated either inside or outside of the container. The present invention also includes a method for hydrogen peroxide vapor sterilization of an article in which the inorganic hydrogen peroxide complex used is one which does not decompose to release a hydrohalic acid.

Yet another aspect of the present invention relates to a method for hydrogen peroxide sterilization of an article using a self-sterilizing enclosure. In this method, the article is placed in a enclosure containing an inorganic hydrogen peroxide complex, the enclosure is sealed, and the enclosure allowed to stand at a temperature below 70°C for a time sufficient to release hydrogen peroxide vapor from the complex and effect sterilization of the article. Although not necessary, the enclosure can be allowed to stand at a pressure less than atmospheric pressure or at a temperature above room temperature (23°C). Thus, the enclosure can be allowed to stand at a temperature below about 40°C. Any of a variety of enclosures can be used, e.g. a pouch, a container, a chamber or a room. Preferably, the hydrogen peroxide complex is in the form of a powder or tablet. The sealing step can include sealing the enclosure with a gas permeable material, such as TYVEK™, CSR wrap, or paper.

REPLACEMENT SHEET
08 APR 1997

The present invention also relates to a sealed enclosure containing a sterile product and an inorganic hydrogen peroxide complex capable of releasing hydrogen peroxide vapor.

Included within the present invention is also a potassium pyrophosphate hydrogen peroxide complex.

A further aspect of the invention relates to a method for hydrogen peroxide sterilization of an article having an exterior and a narrow lumen therein. This method involves connecting a vessel containing an inorganic peroxide complex to the lumen of the article, placing the article within a container, whereby the vessel remains connected to the lumen, reducing the pressure within the container, and contacting the lumen of the article with hydrogen peroxide vapor released from the inorganic peroxide complex at a temperature less than 70°C.

Brief Description of the Drawings

FIGURE 1 is a schematic of a vapor sterilization apparatus of the present invention.

FIGURE 2 is a schematic of a vapor sterilization apparatus of the present invention which includes an electrode which is optionally used to generate plasma.

FIGURE 3A is a schematic of a device which can be used for heating peroxide complexes.

FIGURE 3B is a schematic of a preferred container for holding the peroxide source for sterilization according to the present invention.

FIGURE 4 is a graph depicting the release of hydrogen peroxide vapor from a vacuum unstable non-aqueous hydrogen peroxide complex.

FIGURE 5 is a schematic of a pressure control system of a differential scanning calorimeter (DSC) used to determine hydrogen peroxide release or decomposition properties of inorganic peroxide complexes according to the present invention.

FIGURE 6 is a graph showing the effect of pressure on hydrogen peroxide release from potassium oxalate peroxide complex.

REPLACEMENT SHEET
08 APR 1997

FIGURE 7A is a schematic view of a bellows for injecting peroxide vapor into a chamber in accordance with the present invention before injection of the peroxide vapor.

FIGURE 7B is a schematic view of the bellows of FIGURE 7A showing a heated plate in contact with a peroxide complex during injection.

Detailed Description of the Invention

Hydrogen peroxide sterilizers that have been used in the past invariably used an aqueous solution of hydrogen peroxide as their source of sterilant. These sterilizers have disadvantages caused by the presence of water in the system. At higher pressure, such as atmospheric pressure, the excess water in the system can cause condensation. This requires that an extra step be performed to reduce the relative humidity of the atmosphere in an enclosure to be sterilized to an acceptable level before the aqueous hydrogen peroxide vapor is introduced. These sterilizers also have drawbacks caused by the facts that water, having a higher vapor pressure, vaporizes more quickly than hydrogen peroxide from an aqueous solution; and water, having a lower molecular weight, diffuses faster than hydrogen peroxide. When a medical device or the like is enclosed in a sterilizer, the initial sterilant that reaches the device from the hydrogen peroxide source is diluted in comparison to the concentration of the source. The dilute sterilant can be a barrier to sterilant that arrives later, particularly if the device being sterilized is an article, such as an endoscope, that has narrow lumens. Using a concentrated solution of hydrogen peroxide as the source in an attempt to overcome these drawbacks is unsatisfactory, because such solutions are hazardous.

In the present invention, the shortcomings of hydrogen peroxide sterilizers of the prior art are overcome by using a substantially non-aqueous (i.e., substantially anhydrous) source of hydrogen peroxide which releases a substantially non-aqueous hydrogen peroxide vapor. In a preferred embodiment, the substantially non-aqueous hydrogen peroxide vapor is produced directly from a substantially nonaqueous hydrogen peroxide complex. However, the substantially non-aqueous hydrogen peroxide vapor can also be

generated from an aqueous complex which is processed during vaporization to remove water, such as under vacuum. Thus, where an aqueous hydrogen peroxide complex is used, the aqueous complex can be converted to a substantially non-aqueous hydrogen peroxide complex while carrying out the process of the present invention. Preferably, the substantially non-aqueous hydrogen peroxide complexes contain less than about 20% water, more preferably no more than about 10% water, still more preferably no more than about 5% water, and most preferably no more than about 2% water.

As is apparent from the preferred percentages of water in the substantially non-aqueous hydrogen peroxide complexes used in the present invention, as provided above, the most preferred hydrogen peroxide complex and the peroxide vapor generated therefrom are substantially water-free. Nevertheless, as is also apparent from these figures, some water can be present in the system. Some of this water may derive from the decomposition of hydrogen peroxide to form water and oxygen as byproducts and some hydrogen binding of this water to the complex can occur.

The effect of water was measured in a series of tests, with a sterilization chamber maintained at various relative humidities. Test conditions were those described in Example 1, below, with spores supported on stainless steel (SS) blades in 3mm x 50cm stainless steel lumens. As shown in Table 2, under the test conditions, 5% relative humidity has no effect on efficacy but 10% relative humidity decreases the sterilization rate. This example shows that small amounts of moisture can be allowed in the system with the hydrogen peroxide generated from the non-aqueous peroxide complex and the presence of water in the system can be overcome by increasing the exposure time.

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Table 2

Effects of Relative Humidity on Efficacy
SS Blades in 3mm x 50cm SS Lumens

Diffusion Time	Sterility Results (Positive/Samples)		
	1%RH	5%RH	10%RH
5	0/3	0/3	3/3
10	0/3	0/3	2/3
15	0/3	0/3	0/3
30	0/3	0/3	0/3

A primary criterion for the composition of the hydrogen peroxide source is the relationship between its stability and hydrogen peroxide evaporation rate as a function of temperature and pressure. Depending on the parameters of the sterilization process—e.g. pressure, temperature, etc.—a higher or lower peroxide evaporation rate may be preferred, and heating the peroxide source may or may not be required. The need for heating of the peroxide complex depends on the vapor pressure of the complex. Some peroxide complexes have a sufficiently high vapor pressure that a significant amount of hydrogen peroxide vapor can be released without heating the complex. In general, heating the complex increases the vapor pressure of hydrogen peroxide and accelerates the release of peroxide from the complex.

To provide a desirably high evaporation rate, the source should preferably have a large surface area. Thus the source may be a fine powder or a coating on a material that has a large surface area. Of course, safety, availability, and cost of the material are also important criteria. The release of hydrogen peroxide from hydrogen peroxide complexes with urea, polyvinylpyrrolidone, nylon-6, glycine anhydride, and 1,3 dimethyl urea were evaluated. The complexes of hydrogen peroxide with urea, polyvinylpyrrolidone, nylon-6, and glycine anhydride are solids. The 1,3 dimethyl urea peroxide complex is a liquid. The glycine anhydride hydrogen peroxide complex is a less stable complex under reduced pressure than the

other complexes evaluated, and under vacuum conditions, most of the hydrogen peroxide can be released from the complex without the need for additional heating.

Urea hydrogen peroxide complex is available in tablet form from Fluka Chemical Corp., Ronkonkoma, NY and in powder form from Aldrich Chemical Co., Milwaukee, WI. This complex is also known as urea peroxide, hydrogen peroxide urea complex, peroxide urea, peroxide urea adduct, urea peroxide adduct, percarbamide, carbamide perhydrate, and carbamide peroxide. As used herein, the term "urea peroxide" encompasses all of the foregoing terms.

The polyvinylpyrrolidone-hydrogen peroxide complex (PVP-H_2O_2) can be prepared by the method disclosed in International Application Pub. No. WO 92/17158. Alternatively, the complexes with PVP, with nylon-6, with 1,3 dimethylurea and with glycine anhydride, as well as with other organic and inorganic compounds can be prepared by the method disclosed in detail below.

Achieving suitable evaporation rates of anhydrous peroxide vapor from the source may be facilitated by elevated temperatures and/or reduced pressure. Thus, a heater for the peroxide source and/or a vacuum pump to evacuate the sterilization chamber are preferably a part of the sterilizer. Preferably, the source is covered with a layer of gas permeable material, such as TYVEK™ nonwoven polyethylene fabric, nonwoven polypropylene such as SPUNGUARD™, or similar material, which permits the peroxide vapor to pass but not the peroxide complexing material. Perforated aluminum or other suitable perforated material could also be used as a cover.

FIGURE 3A shows a device 80 that can be used to measure release of hydrogen peroxide from hydrogen peroxide complexes under various temperature conditions. In this device, an aluminum pan 90 is covered with a gas permeable layer 92, such as a layer of medical grade TYVEK™. The pan 90 is placed on top of a heating pad 94 which is placed in a pyrex pan 96. A thermocouple thermometer 98 is placed on the outside of the pan 90 approximately 1 cm from the bottom thereof.

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

A preferred container 99 for holding the peroxide source is illustrated in FIGURE 3B. The container 99 comprises a metal plate 100, e.g. an aluminum plate, with an optional attached heater used to heat the solid peroxide complex. A temperature monitor 101, such as a thermometer, can be placed on the plate 100 to monitor the temperature. The peroxide complex is placed directly on the plate 100. Alternatively, in order to provide even heating of all the peroxide complex, the peroxide complex can be placed between one or more aluminum screens 102, 104 placed on top of the plate 100. The aluminum screens 102, 104 provide greater surface area and even heating of the complex when larger amounts of peroxide complex are being used. The peroxide complex, or the screen or screens 102, 104, are then covered with a gas permeable layer 106, such as a layer of medical grade TYVEK™ or SPUNGUARD™, so that the hydrogen peroxide released from the complex passes through the covering 106 before diffusing into the rest of the chamber. A perforated aluminum plate 108 is optionally placed on top of the TYVEK™ or SPUNGUARD™ layer 106 to provide pressure to keep the complex in contact with the heated plate 100 and to ensure even heating of the peroxide complex.

The device just described provides even heating of the complex, which results in an increased amount of hydrogen peroxide vapor being released from the peroxide complex.

FIGURE 1 depicts a schematic of a hydrogen peroxide vapor sterilization apparatus of the present invention. Chamber 10 holds an article 12 which is to be sterilized and which, for convenience, is placed on shelf 14. Door 16 provides access to the interior of chamber 10. A non-aqueous source of hydrogen peroxide 18 is depicted on optional heater 20, which is controlled by temperature controller 22. The peroxide concentration can be monitored by optional monitor 24. If desired, chamber 10 can be evacuated using pump 26; however, sterilization can also be accomplished at atmospheric pressure.

The container that holds the articles to be sterilized can be a conventional sterilization chamber, which is evacuated, or it can be a container (or a room) at atmospheric pressure.

REPLACEMENT SHEET
08 APR 1997

The time required to sterilize the articles depends on the nature, number and packaging of the articles and their placement in the chamber. Alternatively, it may be the chamber itself (or an entire room) that is being sterilized. In any case, optimum sterilization times can be determined empirically.

The use of pressure pulsing to enhance the penetration and antimicrobial activity of sterilant gases, which is well known in the sterilization art, can also be applied to the non-aqueous hydrogen peroxide process. As described in additional detail hereinbelow, plasma can also be used to further enhance activity.

At the conclusion of the sterilization process excess hydrogen peroxide can be removed from devices that have an affinity for peroxide by exchanging the air in contact with the devices. This can be accomplished by flowing warm air over the devices for an extended time or by evacuating the chamber.

Articles that have previously been sterilized by exposure to hydrogen peroxide vapor may also be exposed to the plasma to remove residual hydrogen peroxide that may remain on the articles. Since the hydrogen peroxide is decomposed into non-toxic products during the plasma treatment, the sterilized articles may be used without the need for any additional steps.

It may be desirable to isolate the peroxide source from the sterilizer after the peroxide vapor is released to avoid reabsorption of the vapor or, when a plasma is used, to avoid exposing the source to the plasma. Isolation is also advantageous when the complex used is not stable under vacuum. Isolation can be accomplished using valves or other isolating devices well known in the art.

FIGURE 2 depicts a schematic of a hydrogen peroxide plasma sterilization system of the present invention. Sterilization can be achieved with or without the use of plasma. The plasma can be used to enhance the sporicidal activity of the peroxide vapor, and/or to remove any residual hydrogen peroxide remaining on the sterilized articles.

REPLACEMENT SHEET
08 APR 1997

Sterilization is carried out in chamber 30, which includes a door or opening 32 through which articles to be sterilized can be introduced. The chamber 30 includes an outlet 34 to a vacuum pump 36, through which the chamber can be evacuated. The outlet 34 contains a valve 38 to isolate the chamber from the vacuum pump 36. The chamber 30 also includes an inlet 40 attached to an enclosure 42 that contains the hydrogen peroxide complex. Inlet 40 contains a valve 44 that allows enclosure 42 to be isolated from the chamber. The sterilization system also contains an inlet 41 which connects the enclosure 42 and the vacuum pump 36, which contains a valve 43. This system allows the simultaneous evacuation of both enclosure 42 and chamber 30, or the independent evacuation of either enclosure 42 or chamber 30. Evacuation is controlled by the opening and closing of the valves 38, 44, and 43. As will be apparent to one having ordinary skill in the art, two pumps, one for each chamber, could also be employed in this system.

The enclosure 42 contains an optional heater 49 attached to a temperature controller 46 to control the temperature of the hydrogen peroxide complex. The hydrogen peroxide complex concentration in the vapor state can be monitored by an optional peroxide monitor 48. The interior of the chamber contains a radio frequency (RF) electrode 50, to which is attached a matching network 52 and an RF power supply 54. A convenient form for the electrode is a perforated cylinder, surrounding the samples and open at both end. The general operation of the present process is as follows:

1. The articles 56 to be sterilized are placed in the chamber 30.

2. The chamber 30 may be at atmospheric pressure or, alternatively, may be evacuated to facilitate penetration of the hydrogen peroxide. Evacuation is accomplished by opening valve 38 and turning on vacuum pump 36. Alternatively, both the chamber 30 and the enclosure 42 may be evacuated by opening valves 38 and 44, and/or 43.

3. The valves 38 and 43 are closed to isolate the vacuum pump 36 from the chamber 30 and enclosure 42, and the valve 44 is opened. Hydrogen peroxide vapor is delivered into chamber 30 from the hydrogen peroxide

REPLACEMENT SHEET
08 APR 1997

source, which may be heated to facilitate the release of the hydrogen peroxide vapor. Optionally, air or an inert gas may also be added.

4. The articles 56 to be sterilized are either treated with peroxide vapor until sterilized or pretreated with peroxide vapor in the chamber 30 before plasma with sufficient power to sterilize is generated. If necessary, chamber 30 may be evacuated at this time to facilitate generation of the plasma. The duration of the pre-plasma holding period depends on the type of package used, the nature and number of items to be sterilized, and the placement of the items in the chamber. Optimum times can be determined empirically.

5. The articles 56 are subjected to a plasma by applying power from the RF power supply 54 to the RF electrode 50. The RF energy used to generate the plasma may be pulsed or continuous. The articles 56 remain in the plasma for a period to effect complete sterilization and/or to remove residual hydrogen peroxide. In certain embodiments, 5 to 30 minutes of plasma is used. However, optimum times can be determined empirically.

When used in the present specification and claims, the term "plasma" is intended to include any portion of the gas or vapor that contains electrons, ions, free radicals, dissociated and/or excited atoms or molecules produced as a result of an applied electric field, including any accompanying radiation that might be produced. The applied field may cover a broad frequency range; however, a radio frequency or microwaves are commonly used.

The non-aqueous hydrogen peroxide delivery system disclosed in the present invention can also be used with plasmas generated by the method disclosed in the previously mentioned U.S. Pat. 4,643,876. Alternatively, it may be used with plasmas described in U.S. Patent 5,115,166 or 5,087,418, in which the article to be sterilized is located in a chamber that is separated from the plasma source.

The device just described is particularly advantageous when using peroxide complexes that are not stable under vacuum. There are at least two possible methods that can be used to minimize the loss of hydrogen peroxide during the vacuum stage. First, the small chamber can be evacuated

REPLACEMENT SHEET
08 APR 1997

independently. Second, if a small enough chamber is used, there is no need to evacuate the small chamber at all.

One such unstable non-aqueous peroxide complex is glycine anhydride-peroxide. This compound releases hydrogen peroxide vapor when placed under vacuum. FIGURE 4 is a graph illustrating the release of hydrogen peroxide vapor from glycine anhydride-peroxide complex under vacuum. The procedure used to release the hydrogen peroxide from the glycine anhydride complex is as follows: (1) The main chamber 30 was evacuated with valves 43 and 44 closed. (2) The chamber containing the hydrogen peroxide complex 42 was evacuated with valves 38 and 44 closed and valve 43 open. (3) Valve 43 was closed and valve 44 was opened and hydrogen peroxide vapor was allowed to diffuse into chamber 30.

As shown by the graph, hydrogen peroxide vapor is released from the complex as the pressure is reduced, even without additional heating. As illustrated in FIGURE 4, release of peroxide vapor is significantly increased by heating the complex to a higher temperature. Thus, even unstable peroxide complexes are useful in the sterilization method of the present invention.

The present invention provides at least four advantages over earlier hydrogen peroxide sterilization systems:

1. The use of concentrated, potentially hazardous hydrogen peroxide solutions is circumvented.

2. The need to reduce beforehand the relative humidity of areas to be sterilized in order to prevent condensation is eliminated.

3. Water is substantially eliminated from the system, so that there is little competition between water and hydrogen peroxide for diffusion into long narrow lumens.

4. The need to attach a special vessel to deliver sterilant gases into long narrow lumens can often be eliminated.

That sterilization can be effected using hydrogen peroxide vapor in the substantial absence of moisture is one of the surprising discoveries of the present invention. The prior art teaches that the presence of water is required

to achieve sterilization in chemical gas or vapor state sterilization processes. Advantageously, the present invention substantially eliminates water from the system, which results in faster, more efficient and effective sterilization.

The sterilization efficacy of various non-aqueous hydrogen peroxide complexes was determined as described below in Examples 1-4.

Example 1

Efficacy data was obtained with hydrogen peroxide vapor released from substantially anhydrous urea peroxide complex using *Bacillus subtilis* var. *(niger)* spores in metal and TEFLON™ plastic lumens as the biological challenge.

A. Test Procedures

1. **Equipment**

Four grams of crushed hydrogen peroxide urea adduct tablet (Fluka Chemical Corp, Ronkonkoma, NY) were placed in an aluminum pan 90, as described in FIGURE 3A. The top of the pan 90 was covered with medical grade TYVEK™ 92 (a breathable spunbond polyethylene fabric) so that any hydrogen peroxide released from the complex would need to pass through the TYVEK™ covering before diffusing into the rest of the chamber. The aluminum pan 90 was placed on a heating pad 94 in a pyrex dish 96 located in the bottom of an aluminum sterilization chamber (see FIGURE 1). The sterilization chamber, which had an approximate volume of 173 liters, also contained:

- A hydrogen peroxide monitor for measuring hydrogen peroxide concentration in the vapor phase.
- A temperature controller for controlling the temperature of the heating pad.
- An injection port through which liquid hydrogen peroxide could be injected into the chamber.
- A metal shelf on which a plastic tray containing lumen devices were placed for testing.

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Electrical resistance heaters on the exterior of the chamber walls, which maintained the chamber temperature at 45°C during the efficacy testings.

2. **Biological Challenge and Test**

To evaluate the efficacy of the non-aqueous peroxide delivery system, a biological challenge consisting of 1.04×10^6 *B. subtilis* var. *(niger)* spores on a stainless steel scalpel blade was placed equally distant from each end of the stainless steel lumens of dimensions 3mm ID × 40cm length, 3mm ID × 50cm length, and 1mm ID × 50cm length. These ID's and lengths are typical for metal lumens used in medical devices. The compartment in the middle of each lumen that contained the biological test piece had the dimensions 13mm ID × 7.6cm length. In the biological testing with metal lumens, a total of 9 lumens were evaluated per test. These included 3 lumens from each of the 3 different sets of ID's and lengths available.

Similar tests were conducted with a biological challenge consisting of 4.1×10^5 *B. subtilis* var. *(niger)* spores on a paper strip (6mm × 4mm Whatman #1 chromatography paper) located equally distant from the ends of TEFLON™ lumens of dimensions 1mm ID × 1 meter length, 1mm ID × 2 meter length, 1mm ID × 3 meter length, and 1mm ID × 4 meter length. The center compartment of these lumens that contained the biological test piece had the dimensions 15mm ID × 7.6cm length. In the biological testing with TEFLON™ lumens, a total of 12 lumens were evaluated per test, 3 lumens from each of the 4 different lengths available.

The lumens containing the biological test samples were placed in a plastic tray that was then placed on the shelf in the sterilization chamber. The chamber door was then closed and the chamber evacuated to 0.2 Torr pressure with a vacuum pump. The aluminum pan containing the hydrogen peroxide urea adduct was then heated to 80 to 81°C for a period of 5 minutes, as measured by a thermocouple thermometer placed on the side wall of the aluminum pan approximately 1 cm from the bottom of the pan. During this time

the concentration of hydrogen peroxide in the chamber increased to 6mg/L as measured by the peroxide monitor.

The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5, 10, 15, 20, and 25 minutes. After exposure to the hydrogen peroxide vapor, the biological test samples were aseptically transferred into 15mL of trypticase soy broth containing 277 units of catalase to neutralize any hydrogen peroxide residuals that may remain on the test samples. All samples were incubated for 7 days at 32°C and observed for growth.

Comparative studies were also conducted in which a 50% aqueous solution of hydrogen peroxide was injected into the sterilization chamber and vaporized from a heated injector (a heated metal surface). The volume of hydrogen peroxide solution injected produced a vapor phase concentration of hydrogen peroxide of 6mg/L. The test lumens and biological test samples used in these tests were identical to those used in the non-aqueous hydrogen peroxide tests. The handling of the biological test samples after exposure to the hydrogen peroxide was also identical.

B. Test Results

The results of these tests with stainless steel and TEFLON™ lumens, which are presented in Tables 3 and 4, respectively, illustrate the advantages of the non-aqueous peroxide delivery system with both metal and non-metal lumens. Total kill of the bacterial spores was achieved within 5 minutes with the non-aqueous peroxide delivery system for the smallest ID and the longest lumens evaluated. At the same time, total kill was not achieved even after 25 minutes of diffusion time with the 50% hydrogen peroxide solution.

REPLACEMENT SHEET
08 APR 1997

Table 3

Aqueous/Non-Aqueous Efficacy Comparison
SS Blades in SS Lumens

SOURCE OF PEROXIDE	DIFFUSION TIME (MIN)	STERILITY RESULTS (POSITIVE/SAMPLES) 3mm × 40cm	3mm × 50cm	1mm × 50cm
50% SOLUTION	5	3/3	3/3	3/3
	10	0/3	2/3	3/3
	15	1/3	1/3	1/3
	20	0/3	0/3	1/3
	25	0/3	0/3	1/3
UREA PEROXIDE	5	0/3	0/3	0/3
	10	0/3	0/3	0/3
	15	0/3	0/3	0/3
	20	0/3	0/3	0/3
	25	0/3	0/3	0/3

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Table 4

Aqueous/Non-Aqueous Efficacy Comparison
6mm x 4mm Paper strip in TEFLON™ Lumens

SOURCE OF PEROXIDE	DIFFUSION TIME (MIN)	STERILITY RESULTS (POSITIVE/SAMPLES) 1mm x 1m	1mm x 2m	1mm x 3m	1mm x 4m
50% SOLUTION	5	3/3	3/3	3/3	3/3
	10	3/3	3/3	3/3	3/3
	15	0/3	1/3	1/3	2/3
	20	0/3	0/3	1/3	1/3
	25	0/3	0/3	0/3	1/3
UREA PEROXIDE	5	0/3	0/3	0/3	0/3
	10	0/3	0/3	0/3	0/3
	15	0/3	0/3	0/3	0/3
	20	0/3	0/3	0/3	0/3
	25	0/3	0/3	0/3	0/3

The fact that rapid sterilization can be accomplished in the absence of substantial amounts of water is surprising, in light of the fact that moisture has generally been present during chemical gas/vapor phase sterilization by various sterilants other than hydrogen peroxide. Since vapor phase hydrogen peroxide sterilization systems have used aqueous solutions of hydrogen peroxide, there has been moisture present in those systems as well.

To test the sterilization efficacy of various other peroxide complexes, the following experiments were performed.

Examples 2, 3 and 4

The apparatus of Example 1 was used to test the efficacy of polyvinylpyrrolidone-hydrogen peroxide complex (Example 2), nylon 6-hydrogen peroxide complex (Example 3), and 1,3 dimethylurea hydrogen peroxide complex (Example 4). These compounds were synthesized according to the

REPLACEMENT SHEET
08 APR 1997

method disclosed below in Examples 12 and 13. Test parameters were as follows:

	Example 2	Example 3	Example 4
Chamber Temp.	45°C	45°C	45°C
Initial Pressure	0.2 Torr	1.0 Torr	1.0 Torr
Wt. % of peroxide	17%	10.5%	26.6%
Peroxide concentration	6mg/L	6mg/L	6mg/L
Wt. of complex used per cycle	8g	18g	6g
Temp to release peroxide	110°C	110°C	80°C

In each case, spore supports were 6mm × 4mm paper substrates in plastic lumens and stainless steel blades in stainless steel lumens. The results of this efficacy testing appear below in Table 5.

Table 5

Efficacy of Complexes with PVP, nylon 6, and 1,3-dimethylurea

		STERILITY RESULTS (POSITIVE/SAMPLES) With 5 Minutes Exposure		
TYPE OF LUMEN	SIZE OF LUMENS	Example 2	Example 3	Example 4
TEFLON™	1mm × 1m	0/3	0/3	0/3
	1mm × 2m	0/3	0/3	0/3
	1mm × 3m	0/3	0/3	0/3
	1mm × 4m	0/3	0/3	0/3
STAINLESS STEEL	3mm × 40cm	0/3	0/3	0/3
	3mm × 50cm	0/3	0/3	0/3
	1mm × 50cm	0/3	0/3	0/3

REPLACEMENT SHEET
08 APR 1997

The results appearing in Table 5 show that each of the tested hydrogen peroxide complexes generate peroxide vapor which provides efficient sterilization after only five minutes exposure.

The temperature required to release the hydrogen peroxide vapor from the solid complex which is shown above is the temperature measured by a thermocouple thermometer located on the outside of the aluminum pan approximately 1 cm from the bottom of the pan. Further testing using a thermometer, such as a fluoroptic thermometer, placed on the inside bottom of the pan indicated that the temperature at the bottom of the pan was approximately 30-35°C higher, as described in Example 5 below. Thus, in the previous example, the temperature at the bottom of the pan was approximately 110 -115°C when the thermocouple thermometer read 80°C, and the temperature at the bottom of the pan was approximately 140 -145°C when the thermocouple thermometer read 110°C.

Example 5

To determine the temperature at the bottom of the aluminum pan used to contain the solid peroxide complex, a fluoroptic thermometer was taped to the inside bottom of the aluminum pan. An Omega™ thermocouple thermometer was placed on the outside of the aluminum pan approximately 1 cm from the bottom of the pan. Three different readings of the thermometers were taken. Each time the pan was heated to the desired temperature indicated by the thermometer placed on the side of the pan, allowed to cool, and then re-heated to the desired temperature. The recorded temperatures are listed below:

Temp. at side of pan	Temp. at bottom of pan (°C) 1st	2nd	3rd	avg
80°C	110.9	110.6	110.6	110.7
100°C	131.5	132.6	132.0	132.0

REPLACEMENT SHEET
08 APR 1997

The results show that the temperature at the bottom of the aluminum pan was approximately 30-35°C higher than the temperature indicated by the thermocouple thermometer located at the side of the pan.

Further testing was performed to compare the efficacy data obtained using an aqueous and non-aqueous source of peroxide in an open (non-lumen) system. The experiments are described in detail below.

Example 6

The apparatus of Example 1 was used with a biological challenge that consisted of 6.8×10^5 *B. subtilis* var *(niger)* spores on a 6mm × 4mm strip of Whatman #1 chromatography paper packaged in a TYVEK™/MYLAR™ envelope. (TYVEK™ is a gas permeable fabric made of polyethylene. MYLAR™ is a non-gas permeable polyester material). Packaged biological challenge strips were placed in the front, middle and back of a polyphenylene oxide tray that contained a flexible fiberoptic sigmoidoscope. The tray was placed in a polyphenylene oxide container that had one port in the top and two ports in the bottom to allow for diffusion. The four-inch diameter ports were covered with a breathable polypropylene packaging material (SPUNGUARD™ Heavy Duty Sterilization Wrap, Kimberly-Clark, Dallas, TX) to maintain the sterility of the contents of the container after sterilization. The container was placed in the apparatus of Example 1 and the pressure in the chamber was reduced to 0.2 Torr. The aluminum pan containing 2 grams of hydrogen peroxide urea adduct (Fluka Chemical Corp.) was then heated to 80 to 81°C, as measured by a thermocouple thermometer placed on the outside of the aluminum pan approximately 1 cm from the bottom of the aluminum pan, for 5 minutes to provide 3mg/L of hydrogen peroxide vapor in the chamber. The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5 and 10 minutes. After exposure the test samples were handled in the same way as were those in Example 1.

Comparative studies were also conducted in which a 50% aqueous solution of hydrogen peroxide was injected into the sterilization chamber and vaporized from a heated injector. The volume of hydrogen peroxide solution

REPLACEMENT SHEET
08 APR 1997

injected produced a vapor phase concentration of 3mg/L. The test configuration, the composition of the biological test samples, and the handling of the biological test samples after exposure were all identical to those used in the non-aqueous hydrogen peroxide tests. The results of these tests are presented in Table 6.

Table 6

Aqueous/Non-Aqueous Efficacy Comparison in Open System (Non-Lumen Test)

Source of Peroxide	Diffusion Time (min)	Sterility Results (positive/samples)
50% solution	5	3/3
	10	3/3
Urea Peroxide	5	1/3
	10	0/3

The results of these tests demonstrate the greater efficacy of the non-aqueous when compared with the aqueous hydrogen peroxide process in an "open" system in which the biological sample was not placed in a lumen. Again, it was surprisingly discovered that a non-aqueous system provided superior sterilization even when diffusion of hydrogen peroxide into a long and narrow lumen is not required. This suggests that the mode of action of hydrogen peroxide is not the same for systems with and without water.

Further testing was performed to determine the efficacy a non-aqueous peroxide vapor at normal, not reduced, pressure. This testing is detailed below.

Example 7

Efficacy tests were conducted with the hydrogen peroxide vapor released from the urea peroxide complex in an open system at atmospheric pressure. In this test the biological challenge of 1.04×10^6 *B. subtilis* var. *(niger)* spores on the stainless steel surgical blades were packaged in a TYVEK™/MYLAR™

REPLACEMENT SHEET
08 APR 1997

envelope. Packaged biological challenge blades were placed on the front, middle, and back of a polyphenylene oxide tray. The tray was placed in the apparatus of Example 1 and the chamber door was closed. The aluminum pan containing 4.0 gm of urea peroxide (Fluka Chemical Corp.) was heated to 80° to 81°C, as measured by a thermocouple thermometer placed on the side of the aluminum pan approximately 1 cm from the bottom of the pan, for the duration of the test. The biological test samples were exposed to the hydrogen peroxide vapor for periods of 5, 10, 20 and 30 minutes. After exposure the test samples were handled the same way as those in Example 1. The results of these tests are presented in Table 7 and demonstrate the efficacy of the non-aqueous peroxide process in an open system at atmospheric pressure.

Table 7

Efficacy of non-aqueous peroxide process in open system at atmospheric pressure

Source of Peroxide	Diffusion Time (minutes)	Sterility Results (positive/samples)
Urea Peroxide	5	3/3
	10	1/3
	20	0/3
	30	0/3

Further tests were conducted to determine the approximate amount of peroxide released from the hydrogen peroxide urea complex at various temperatures. This testing is described in Example 8.

Example 8

Urea peroxide powder, obtained from crushing the commercially available tablets (Fluka Chemical Corp.), was placed between two aluminum screens in an apparatus according to FIGURE 3B having dimensions 12.7 cm

× 12.7 cm. The aluminum plate was then heated and the temperature was monitored using a thermometer located near a corner of the aluminum plate. Table 8 lists the approximate percent of peroxide released at various temperatures after heating for five minutes. The data show that approximately 100% of the peroxide is released from the complex at a temperature of 140°C. Lesser percentages of peroxide are released at lower temperatures.

Table 8

Release of non-aqueous peroxide at various temperatures

Heating Temperature	% Peroxide Released
80°C	~25%
100°C	~65%
120°C	~80%
130°C	~90%
140°C	~100%

Peroxide complexes having the ability to release hydrogen peroxide vapor at room temperature and atmospheric pressure, such as the urea peroxide complex, allows them to be effective for use in various sterilization applications. Not only can they be used in the sterilization apparatus of the present invention described above, the compounds of the present invention can also be used as part of self-sterilizing packaging materials, or applied onto supports such as gauze, sponge, cotton, and the like. The compounds allow for sterilization of sealed packages at room temperature or at elevated temperatures, and are particularly useful for the sterilization of packaged medical or surgical products.

Particular uses of the compounds of the present invention are described in the examples which follow. The peroxide complex used in the following

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

examples was urea peroxide in the form of a tablet (Fluka Chemical Corp.) or in the form of a powder obtained by crushing the tablets.

Example 9

A self-sterilizing pouch was assembled as follows: A surgical scalpel having 3.8×10^5 *B. subtilis* var. *niger* spores on its surface was placed in a sterile petri dish. The dish was placed in a larger petri dish, together with 1 gm urea peroxide complex in either tablet or powder form. The larger petri dish was then inserted into a pouch formed of TYVEK™/MYLAR™ (gas permeable, Table 9), MYLAR™/MYLAR™ (non-gas permeable, Table 10) or Paper/MYLAR™ (gas permeable, Table 10). The pouch was then sealed.

Each pouch was exposed to various temperatures for various time periods, as shown in Tables 9 and 10 below. The biological test samples were evaluated for sterilization as described in Example 1. The results are included in Tables 9 and 10, with a "+" sign indicating bacterial growth.

Table 9
Self-Sterilizing Pouches
With Breathable Barrier (TYVEK™/MYLAR™)

Temperature	Peroxide Type	1 hr.	2 hr.	3 hr.	4 hr.
23°C	powder	+	-	-	-
	tablet	+	+	-	-
40°C	powder	-	-	-	-
	tablet	-	-	-	-
60°C	powder	-	-	-	-
	tablet	-	-	-	-

Table 10 lists the efficacy data for self-sterilizing pouches with (Paper/MYLAR™) and without (MYLAR™/MYLAR™) a breathable barrier. The pouches were assembled as described above, however the peroxide vapor source was urea peroxide in powder form only.

REPLACEMENT SHEET
08 APR 1997

Table 10
Self-Sterilizing Pouches With & Without Breathable Barrier

Temperature	Packaging Type	2 hr.	4 hr.
23°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	+	-
40°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	-	-
60°C	MYLAR/MYLAR	-	-
	Paper/MYLAR	-	-

Results from this testing show that the urea peroxide complex of the present invention included in a pouch with and without a breathable barrier provides effective sterilization to an article inside the pouch in the absence of moisture at room temperature and atmospheric pressure after only 2 to 3 hours. At higher temperatures, sterilization is effected after only one hour.

To determine the efficacy of the sterilization system of the present invention in a closed container, the following experiment was performed.

Example 10

A self-sterilizing container was assembled as follows: A stainless steel support having either 3.8×10^6 *B. subtilis* var. *niger* spores on its surface (Table 11) or having 9.2×10^5 *B. subtilis* var. *niger* spores on its surface (Table 12), was placed inside a small polyethylene (PE) vial having 20 holes (3/16" in size) in its surface. The vial was placed in a larger PE vial, which was covered with either an air tight cap, or a gas permeable layer of SPUNGUARD® (CSR Wrap). Also included in the larger vial was a second PE vial, also having 20 holes (3/16" in size) in its surface. This vial contained 1 gm urea peroxide in either powder or tablet form, and was sealed in either a SPUNGUARD™ (CSR wrap) or TYVEK™ pouch.

Each container was exposed to various temperatures for various time periods, as shown in Tables 11 and 12 below. The biological test samples

were evaluated for sterilization as described in Example 1. The results are included in Tables 11 and 12, with a "+" sign indicating bacterial growth.

Table 11
Self-Sterilizing Containers Without Breathable Window

Temperature	Packaging Type	2 hr.	6 hr.
23°C	Unpackaged tablet	+	-
	C/C* packaged tablet	+	-
	C/C packaged powder	+	-
40°C	Unpackaged tablet	-	-
	C/C packaged tablet	-	-
	C/C packaged powder	-	-
60°C	Unpackaged tablet	-	-
	C/C packaged tablet	-	-
	C/C packaged powder	-	-

* - pouch formed from CSR wrap

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Table 12
Self-Sterilizing Containers With Breathable CSR Window

Temperature	Packaging Type	0.5 hr.	1.0 hr.	1.5 hr.	2.0 hr.	3.0 hr.	4.0 hr.
23°C	Unpackaged tablet		+	+	+	-	-
	Unpackaged powder		+	+	+	-	-
	T/T* packaged tablet		+	+	+	+	-
	T/T packaged powder		+	+	+	-	-
	C/C** packaged tablet		+	+	+	-	-
	C/C packaged powder		+	+	+	-	-
40°C	Unpackaged tablet	-	-	-	-		
	Unpackaged powder	-	-	-	-		
	T/T packaged tablet	+	-	-	-		
	T/T packaged powder	-	-	-	-		
	C/C packaged tablet	-	-	-	-		
	C/C packaged powder	-	-	-	-		
60°C	Unpackaged tablet	-	-	-	-		
	Unpackaged powder	-	-	-	-		
	T/T packaged tablet	-	-	-	-		
	T/T packaged powder	-	-	-	-		
	C/C packaged tablet	-	-	-	-		
	C/C packaged powder	-	-	-	-		

* - pouch formed from TYVEK™
** - pouch formed from CSR wrap

Results from this testing show that the non-aqueous urea peroxide complex included in a container with and without a breathable barrier provides effective sterilization at room temperature after only 3-4 hours. At higher temperatures, sterilization is effected after as little as one half hour.

The non-aqueous peroxide complexes which release peroxide vapor have been found to be useful in the sterilization of articles at room temperature, and more effectively, at higher temperatures. These complexes can be placed in a pouch, container, chamber, room or any area capable of being sealed, where they release peroxide vapor which effectively sterilizes the articles. The complexes can be heated to facilitate the release of vapor, and to provide

REPLACEMENT SHEET
08 APR 1997

sterilization in less time than that required for room temperature sterilization. The compounds of the present invention are therefore useful in a variety of applications where sterilization is desired. Simply by placing the complex in a sealed area containing an article or articles to be sterilized, sterilization can be achieved. By contrast with prior art methods, there is no need for contact with moisture to provide activation of the hydrogen peroxide.

To confirm that sterilization can be effected using non-aqueous peroxide complexes in less time at lower pressures, the following experiment was performed.

Example 11

A self-sterilizing container was assembled as follows: A stainless steel support having 9.2×10^5 *B. subtilis* var. *niger* spores on its surface was placed inside a small PE vial having 20 holes (3/16" in size) in its surface. The vial was placed in a larger PE vial, which was covered with a gas permeable layer of CSR wrap (SPUNGUARD™). Also included in the larger vial was a second PE vial, also having 20 holes (3/16" in size) in its surface. This vial contained 1 gm urea peroxide in either powder or tablet form. The vial was then sealed in a CSR wrap or TYVEK™ pouch.

The large vials were placed in either a 4.5 L sterilization chamber or a 173 L sterilization chamber. Each container was exposed to 100 torr pressure and 23°C temperature for 2 hours, as shown in Table 13. The biological test samples were evaluated for sterilization as described in Example 1. The results are included in Table 13.

Table 13
Self-Sterilizing Containers With Breathable Window In Reduced Pressure Conditions

Temperature	Packaging Type	4.5 L chamber	173 L chamber
23°C	Unpackaged powder	-	-
	T/T packaged powder	-	-
	C/C packaged powder	-	-

REPLACEMENT SHEET
08 APR 1997

These results show that non-aqueous urea peroxide complex included in a container with a breathable barrier provides effective sterilization at 100 torr and room temperature after only 2 hours. These results, when compared with the results in Table 12, demonstrate that the peroxide complexes of the present invention provide sterilization at reduced pressures in less time than that required to effect sterilization at atmospheric pressure.

Thus, the hydrogen peroxide complexes of the present invention can provide effective sterilization in significantly shorter periods of time. In addition, as discussed above, plasma can also be used to enhance the sterilization activity of the hydrogen peroxide vapor. The articles to be sterilized are subjected to a plasma after exposure to the peroxide vapor, and remain in the plasma for a period of time sufficient to effect complete sterilization.

Articles that have been sterilized by exposure to hydrogen peroxide vapor can be exposed to a plasma to remove any residual hydrogen peroxide remaining on the articles. Because the residual hydrogen peroxide is decomposed into non-toxic products during the plasma treatment, the sterilized articles are ready for use following treatment, without the need for any additional steps.

Non-aqueous peroxide complexes are useful in a variety of applications, including as a component of self-sterilizing packaging. In addition, the complexes are suitable for use in various methods for vapor sterilization of articles, such as the method disclosed in U.S. Patent No. 4,943,414. This patent discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. The method disclosed in the patent can be modified to allow for use of a non-aqueous peroxide compound. The compound is placed in a vessel and connected to the lumen of the article to be sterilized. The article is then placed within a container and the container evacuated. The lumen of the article and the exterior of the article are contacted by the hydrogen peroxide vapor released from the non-aqueous

REPLACEMENT SHEET
08 APR 1997

compound. A plasma can optionally be generated and used to enhance sterilization and/or to remove any residual hydrogen peroxide form the article.

Use of non-aqueous peroxide complexes in the system just described overcomes the disadvantage that the water in the aqueous solution is vaporized faster and precedes the hydrogen peroxide vapor into the lumen. Thus, more effective sterilization is achieved and less time is required to effect sterilization. Hydrogen peroxide complexes such as glycine anhydride are especially advantageous since they release a significant amount of hydrogen peroxide at reduced pressure without the need for additional heating of the complex.

Synthesis of Non-Aqueous Hydrogen Peroxide Complexes

The present invention further provides a process for preparing non-aqueous hydrogen peroxide complexes that are useful as the source in a hydrogen peroxide vapor sterilizer, or as a component of self-sterilizing packaging, as was described above. Of course, the hydrogen peroxide complexes can be used for other applications, such as for bleaching agents, contact lens solutions, catalysts, and other applications which will be well known by those having ordinary skill in the art.

The general procedure for preparing the hydrogen peroxide complexes of this invention is as follows:

(1) Place the reactant material in the chamber.

The material to be reacted with the hydrogen peroxide can be a solid in various forms, (e.g., powder, crystal, film etc., preferably having high surface area to increase the reaction rate). The reactant material can also be present as a solution in water or another solvent, if sufficient time is allowed to evaporate the solvent after the pressure is reduced in the chamber. The material may also be a liquid whose boiling point is higher than that of hydrogen peroxide (150°C). Since reaction rates are faster at elevated temperature, the chamber is preferably heated whether before or after the reactant composition is introduced. However, the temperature should not be so high that the reactant boils or vaporizes.

REPLACEMENT SHEET
08 APR 1997

The reactant composition may be contained in any container that provides access to the peroxide vapor. If it is in the form of a powder or other form that may be blown about when the chamber is evacuated, then the reactant may be retained in a permeable container, which allows hydrogen peroxide to diffuse into the container.

(2) Evacuate the chamber.

Preferably, the chamber is evacuated to a pressure that is below the vapor pressure of the hydrogen peroxide (which depends on its concentration and temperature), in order to assure that all of the peroxide is in the vapor phase. The vapor pressure increases with increasing temperature and decreases with increasing peroxide concentration. For most of the experiments, the chamber was evacuated to about 0.2 Torr and the temperature was ambient or above.

(3) Generate hydrogen peroxide vapor.

The hydrogen peroxide vapor can be generated from a hydrogen peroxide solution or from a substantially anhydrous hydrogen peroxide complex. The latter yields dry hydrogen peroxide in the vapor state, which is an advantage if either the material to be reacted with the vapor or the complex to be formed is hygroscopic. Another advantage of generating the hydrogen peroxide vapor from a substantially water-free complex is that the percent of hydrogen peroxide in the complex being formed is higher than if the vapor is generated from an aqueous solution of H_2O_2. This is probably due to the competition between water molecules and H_2O_2 molecules for bonding sites on the complex when an aqueous solution is used to generate the H_2O_2 vapor.

The peroxide vapor can be generated within the same chamber that houses the reactant material or in another chamber separated from it by a vacuum valve.

(4) React the reactant material with hydrogen peroxide.

The time required for the reaction depends, of course, on the reaction rate of the reactant with hydrogen peroxide. It can be empirically determined by monitoring the pressure, which decreases during the binding of peroxide to

REPLACEMENT SHEET
08 APR 1997

the reactant material. Typically, the reaction time is about 5-30 minutes. The concentration of vaporized hydrogen peroxide and the weight of the starting material determine the weight percentage of peroxide in the final reaction product. As the weight ratio of reactant to hydrogen peroxide increases, the weight percentage of hydrogen peroxide in the complex decreases. The reaction can be repeated multiple times to increase the concentration of hydrogen peroxide in the complex.

(5) Evacuate the chamber again.

At the end of the reaction period, the chamber is further evacuated to about 2 Torr to remove any unreacted hydrogen peroxide.

(6) Vent the chamber and retrieve the hydrogen peroxide complex.

The mechanism by which the hydrogen peroxide forms a complex with the reactant material is not completely understood. The formation of the complex is believed to involve hydrogen bond formation between the hydrogen peroxide and electron-rich functional groups containing oxygen and/or nitrogen on the reactant material. It is not known if this is the only mode of binding; however, materials with a wide range of functional groups have been found to form complexes with hydrogen peroxide.

The advantages of the vapor phase reaction over earlier methods of hydrogen peroxide complex formation include:

1. The ratio of hydrogen peroxide to reactant material can be accurately controlled by varying the amount of hydrogen peroxide present in the vapor state or the amount of reactant material exposed to the vapor.

2. The need to remove solvent from the reaction product is eliminated.

3. Peroxide complexes can be formed that are liquid or solids, such as powders, crystals, films, etc.

4. Peroxide complexes of hygroscopic materials can be prepared.

The synthesis of the non-aqueous peroxide complexes according to the present invention is further described in the following examples. Many of these compounds have utility as catalysts, in addition to having the utilities described

REPLACEMENT SHEET
08 APR 1997

in greater detail herein, as will be readily appreciated by those having ordinary skill in the art. The examples represent embodiments of the compositions and processes of the invention, but they are not in any way intended to limit the scope of the invention.

Example 12

A hydrogen peroxide complex of glycine anhydride was prepared as follows: A 1.0 gram sample of glycine anhydride (Aldrich Chemical Co., Milwaukee, WI) was placed in an aluminum tray in a 173 liter chamber maintained at a temperature of 45°C. The top of the aluminum tray was covered with TYVEK™ nonwoven fabric, which prevented the glycine anhydride from coming out of the tray when the pressure in the chamber was reduced but was breathable and did not absorb hydrogen peroxide. The chamber door was closed and the pressure in the chamber was reduced to 0.2 Torr by evacuating the chamber with a vacuum pump. A hydrogen peroxide concentration of 10 mg/liter was created by evaporation of an appropriate volume of a 70% aqueous solution of hydrogen peroxide (FMC Corp., Philadelphia, PA) into the chamber. The hydrogen peroxide vapor was maintained in contact with the glycine anhydride for 20 minutes. At the end of the reaction period, the chamber pressure was reduced to 2 Torr and then returned to atmospheric pressure. The reaction product was removed from the chamber and analyzed for weight percent hydrogen peroxide by the following iodometric titration reactions.

$$H_2O_2 + 2KI + H_2SO_4 \longrightarrow I_2 + K_2SO_4 + 2H_2O$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$

A starch indicator was used in the iodine-sodium thiosulfate titration reaction to enhance the color change at the end point. The percentage by weight of hydrogen peroxide was calculated by the following equation:

wt% H_2O_2 = [(ml of $Na_2S_2O_3$)*(normality of $Na_2S_2O_3$) *1.7]/(sample weight in grams)

The weight percentage of hydrogen peroxide in the glycine anhydride complex was found to be 24.3%.

Example 13

The hydrogen peroxide complexes of a wide variety of organic and inorganic complexes were prepared using the procedure of Example 12. In each case, the reaction conditions were the same as those in Example 12, except 1.0 gram of each one of the compounds presented in Table 14 was used in place of glycine anhydride.

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Table 14

COMPOUNDS EVALUATED AND WEIGHT PERCENT HYDROGEN PEROXIDE PRESENT IN COMPLEXES FORMED BY VAPOR PHASE SYNTHESIS PROCESS

Chemical Name	Chemical Structure	Wt% After Peroxide Treatment	Category
Poly(vinyl alcohol)	$[-CH_2CH(OH)-]_n$	18.9%	Alcohol
Poly(vinyl methyl ether)	$[-CH_2CH(OCH_3)-]_n$	22.0%	Ether
Poly(vinyl methyl Ketone)	$[-CH_2-CH(COCH_3)-]_n$	13.9%	Ketone
Poly(acrylic acid)	$[-CH_2CH(COOH)-]_n$	5.1%	Acid
Glycine	$H_2C(NH_2)\ (COOH)$	20.7%	Amino Acid
L-Histidine	$[N{=}CHNHCH{=}C]\ CH_2CH\ (NH_2)\ COOH$	14.1%	Amino Acid
Poly(vinyl acetate)	$[-CH_2CH(OCOCH_3)-]_n$	9.1%	Ester
Cellulose acetate		10.9%	Ester
Sodium alginate		27.7%	Organic Salt
Cellulose sulfate, sodium salt		18.2%	Organic Salt
Poly(4-Vinylpyridine)	$[-CH_2CH(p\text{-}C_5H_4N)-]_n$	21.8%	Aromatic amine
Histamine	$[N{=}CHNHCH{=}C-]\ CH_2CH_2\ (NH_2)$	13.2%	Amine
Propionamide	$(C_2H_5)CONH_2$	31.8%	Amide
Urea	$(H_2N)_2CO$	17.9%	Urea
1,3-dimethylurea	$(H_3C)HNCONH(CH_3)$	31.7%	Urea
Biuret	$(H_2N)CO(NH)CO(NH_2)$	13.7%	Biuret
Polyacrylamide	$[-CH_2CH(CONH_2)-]_n$	30.1%	Polyamide
Polyvinylpyrrolidone	$[-CH_2CH(-N(CH_2)_3CO)-]_n$	29.9%	Polyamide
Nylon 6	$[-NH(CH_2)_5CO-]_n$	17.1%	Polyamide
Nylon 6,6 film	$[-NH(CH_2)_6NHCO(CH_2)_4CO-]_n$	16.6%	Polyamide
Polyetherpolyurethane	$[-RHNCOOR'-]_n$	9.5%	Polyurethane
Sodium carbonate	Na_2CO_3	14.3%	Inorganic
Potassium carbonate	K_2CO_3	33.9%	Inorganic
Rubidium carbonate	Rb_2CO_3	37.0%	Inorganic
Calcium hydroxide	$Ca(OH)_2$	23.4%	Inorganic
Sodium bicarbonate	$NaHCO_3$	10.7%	Inorganic
Tetrasodium pyrophosphate	$Na_4P_2O_7$	18.9%	Inorganic

REPLACEMENT SHEET
08 APR 1997

The organic complexes formed cover the following range of functional groups that are capable of forming hydrogen bonds with hydrogen peroxide: alcohols, ethers, ketones, acids, amino acids, esters, organic salts, amines, amides, polyamides, polyurethanes, ureas, and biuret. The inorganic complexes include carbonates with sodium, potassium, and rubidium cations, as well as sodium bicarbonate. In addition, the hydrogen peroxide complexes of calcium hydroxide and tetrasodium pyrophosphate were also prepared. The starting materials were finely divided powers or slightly larger crystalline materials, except for nylon 6,6, which was processed as a film with a thickness of 0.12 mm, and polyvinyl methyl ether, which was a 50% by weight aqueous solution.

The hydrogen peroxide complexes obtained with these materials under the test conditions were solids, except for polyvinylpyrrolidone, histamine, poly(vinyl methyl ether), poly(vinyl methyl ketone),propionamide, and 1,3-dimethylurea. The 1,3-dimethylurea and propionamide hydrogen peroxide complexes were free flowing liquids that were easily handled in the vapor phase synthesis process, since no solvent needed to be removed to obtain the final product. The histamine, polyvinylpyrrolidone, poly(vinyl methyl ether), and poly(vinyl methyl ketone) complexes were gummy materials that were not as easy to handle.

Examples 14 and 15 describe additional studies with polyvinylpyrrolidone under different process conditions to obtain the peroxide complex as a free flowing solid product.

Example 14

Hydrogen peroxide complexes with polyvinylpyrrolidone were prepared in which the percent hydrogen peroxide in the polyvinylpyrrolidone complex was varied by changing the ratio of the weight of polyvinylpyrrolidone to the concentration of hydrogen peroxide in the vapor state. The conditions in these tests were identical to those in Example 12, except the weight of polyvinylpyrrolidone was increased from 1.0 gram to 3.0 grams to 5.0 grams. In all tests, the concentration of hydrogen peroxide was held constant at 10.0

REPLACEMENT SHEET
08 APR 1997

mg/liter of chamber volume. The results of these tests are presented in Table 15.

Example 15

A hydrogen peroxide complex of PVP was prepared in which the hydrogen peroxide was delivered from a complex of hydrogen peroxide with urea. When hydrogen peroxide is delivered in this manner, it is substantially water free. In this test, 5 grams of PVP was placed in the reaction chamber and 10 mg H_2O_2/liter of chamber volume was delivered into the reaction chamber by heating about 7 grams of a 35% complex of H_2O_2 with urea to a temperature of about 110°C for approximately 5 minutes. The rest of the conditions in this test were the same as those in Example 12. The percentage hydrogen peroxide in the PVP complex and the physical state of the complex are presented in Table 15.

Table 15

EFFECT OF RATIO OF POLYVINYLPYRROLIDONE TO HYDROGEN PEROXIDE IN THE VAPOR STATE ON % HYDROGEN PEROXIDE IN COMPLEX AND PHYSICAL STATE OF PRODUCT

	Weight PVP (g)	Wt% H_2O_2 in Complex	Physical State of Product
Ex. 14	1	29.9	Soft gummy product
	3	23.5	Hard gummy product
	5	17.7	Free flowing solid
Ex. 15	5	19.7	Free flowing solid

The results of these tests demonstrate that a free flowing solid can be obtained with the PVP hydrogen peroxide complex by controlling the ratio of PVP to hydrogen peroxide in the vapor state and, alternatively, by using a substantially water-free hydrogen peroxide vapor source.

INORGANIC HYDROGEN PEROXIDE COMPLEXES

Inorganic hydrogen peroxide complexes are also suitable for use as sterilants as described in detail hereinabove for organic hydrogen peroxide complexes. Peroxide vapor can be released from these inorganic complexes

at atmospheric pressure and room temperature. However, as described in greater detail below, substantial amounts of hydrogen peroxide vapor can be released from inorganic peroxide complexes upon rapid heating to a particular release temperature under reduced pressure. In order to successfully release hydrogen peroxide from inorganic peroxide, the heating rate of the inorganic peroxide complexes is preferably at least 5°C/min; more preferably it is at least 10°C per minute; still more preferably at least 50°C/min.; and most preferably, it is at least 1000°C per minute.

A representative listing of these inorganic peroxide complexes, and the weight percent hydrogen peroxide, is presented in Table 16. The titration procedure used to determine the weight percent of H_2O_2 in the complexes was as described in Example 12. Sodium carbonate H_2O_2 complex was purchased from Fluka Chemical Corp. The vapor-phase synthesis procedure used for synthesizing the inorganic peroxide complexes was the same as that disclosed in Example 12, with the exceptions that 10g of the solid inorganic sample instead of 1-5g, and two reaction cycles versus one, were employed.

Example 16

The reaction procedure for liquid-phase synthesis of inorganic hydrogen peroxide complexes was essentially as described by Jones et al. (*J. Chem. Soc., Dalton*, 12:2526-2532, 1980). Briefly, inorganic solids were first dissolved in a 30% aqueous solution of hydrogen peroxide to make a saturated solution, followed by dropwise addition of ethanol. For the potassium oxalate and rubidium carbonate complexes, the white peroxide precipitates were formed as the amount of ethanol added was gradually increased. For potassium carbonate, potassium pyrophosphate and sodium pyrophosphate, the saturated solutions were incubated at -10°C for several hours to facilitate crystalline peroxide complex formation. The complexes were separated from the liquid by vacuum filtration, washed with ethanol at least three times and dried by vacuum.

REPLACEMENT SHEET
08 APR 1997

Table 16

COMPOUNDS EVALUATED AND WEIGHT PERCENT HYDROGEN PEROXIDE PRESENT IN COMPLEXES

Chemical Name	Chemical Formula	Wt % H_2O_2 in Complexes[1]		
		Purchased[2]	Vapor[3]	Liquid[3]
Sodium Carbonate	Na_2CO_3	27.35		
Potassium Carbonate	K_2CO_3		7.43	22.70
Robidium Carbonate	Rb_2CO_3		20.31	26.78
Potassium Oxalate	$K_2C_2O_4$		16.13	16.42
Sodium Pyrophosphate	$Na_4P_2O_7$		11.48	23.49
Potassium Pyrophosphate	$K_4P_2O_7$		20.90	32.76
Sodium Orthophosphate	Na_3PO_4		15.67	
Potassium Orthophosphate	K_3PO_4		16.11	

1. The titration procedure employed to determine the weight percent of H_2O_2 in the complexes is the same as the one stated in the previous patent application.

2. Sodium carbonate hydrogen peroxide complex was purchased from Fluka Chemical Corp.

3. The vapor and liquid phase procedures were used for synthesizing the inorganic peroxide.

A differential scanning calorimeter (DSC) (Model PDSC 2920, TA instruments) was used to determine H_2O_2 release or decomposition properties of the inorganic peroxide complexes. The DSC was run at a heating ramp of 10°C/min and at a temperature range of between 30°C and 200°C. under both atmospheric and varying vacuum pressure conditions. Referring now to FIGURE 5, the DSC comprises a sample chamber 110, heating plate 112 and pressure control system. The pressure control system comprises a pressure transducer 114 connected to a pressure gauge 116. The pressure gauge 116 is connected to a controller 118 which is, in turn, connected to a pressure control valve 120. The pressure transducer 114 is in fluid communication with pressure control valve 120 and with pump 122.

REPLACEMENT SHEET
08 APR 1997

Potassium oxalate hydrogen peroxide complex synthesized as described hereinabove was placed in a DSC and subjected to a particular vacuum pressure over a temperature range of 50°C to 170°C. As can be seen in FIGURE 6, greater release of H_2O_2, an endothermic process, occurred at lower pressures, while the exothermic decomposition of H_2O_2 was favored at higher pressures. The partial vacuum pressure is preferably less than 20 torr and most preferably less than 10 torr. The actual pressure in the sample chamber is somewhat higher than that measured within the apparatus and the actual temperature of the chamber is somewhat lower than that measured of the metal plate or aluminum platen. Without wishing to be bound by any particular theory of operation, it is believed that the actual pressure used in the sterilization apparatus should be less than the vapor pressure of the inorganic peroxide complex at the actual temperature of the chamber in order to ensure that the complex will release hydrogen peroxide vapor with substantially no decomposition. However, in general, the pressure used is preferably less than 50 torr, more preferably less than 10 torr. In certain embodiments of the invention in which the vapor pressure of the peroxide complex is low, the pressure is preferably less than 5 torr.

In the use of the inorganic peroxide complexes for sterilization, it is critical to complex stability that heating occur rapidly which may be effected by preheating the aluminum plate prior to contacting with the inorganic peroxide composition. In the use of the inorganic peroxide compounds, it is also preferred that the temperature be higher than 86°C.

As discussed above, it is preferred that the inorganic hydrogen peroxide complex be heated rapidly, i.e. as rapidly as 1000°C/minute or more. This can be accomplished by contacting the peroxide with a pre-heated heating plate. A preferred embodiment for accomplishing such rapid heating is shown in FIGURES 7A and 7B. Referring to FIGURE 7A, there is shown an apparatus 125 for injecting peroxide vapor into a sterilization chamber 131 in a closed position. The inorganic hydrogen peroxide complex is incorporated into a peroxide disk 132. The disk 132 comprises five layers: three layers of CSR

REPLACEMENT SHEET
08 APR 1997

wrap, peroxide complex powder and aluminum foil coated with polypropylene. The disk 132 is heat sealed around its edge to retain the peroxide complex powder. The peroxide disk 132 is placed underneath a perforated aluminum plate 130 which is attached to housing 150 by aluminum attachment pieces 142. The disk 132 is loosely held in place between O-rings 151. Prior to introduction of peroxide vapor into the chamber, a heated aluminum platen 134 is apart from the peroxide disk 132 and is attached to an aluminum plate 136. A spring (not shown) within the bellow 138 holds the plate 136 down in the closed position. When the chamber 131 is evacuated, the bellow 138 is also evacuated. The plate 136 is seated against O-rings 148, thus separating a peroxide release chamber 152 from passageways 158. The apparatus is held in place and attached to a sterilization chamber 131 by bolts 144, 146, 154 and 156.

Referring to FIGURE 7B, in order to bring the platen 134 up to contact the peroxide disk 132, the bellow 138 is vented. Once the pressure is increased, the bellow 138 moves upward, thereby propeling the heated aluminum platen 134 against the peroxide disk 132. In a preferred embodiment, the aluminum platen 134 is pre-heated to 175°C; however other temperatures can be used. Peroxide vapor is then released from the powder through the CSP layers, passes through the perforations 160 in the perforated aluminum plate 130, and enters the peroxide release chamber 152. The upward movement of the heated aluminum platen 134 also opens the peroxide release chamber 152, allowing peroxide vapor to enter passageways 158 which are in fluid communication with the sterilization chamber.

The inorganic peroxide complexes used in the following two examples to determine amount of peroxide release and sterilization efficacy were potassium pyrophosphate ($K_4P_2O_7 \cdot 3H_2O_2$: PP), potassium oxalate ($K_2C_2O_4 \cdot 1H_2O_2$: PO) and sodium carbonate ($Na_2CO_3 \cdot 1.5\ H_2O_2$: SC).

REPLACEMENT SHEET
08 APR 1997

Example 17

Release of Peroxide from SC, PO and PP

The ideal temperature at which H_2O_2 was released from SC, PO and PP was determined by DSC. The actual amount of H_2O_2 released from 2 g of each of these complexes was determined at various temperatures using a 75 liter chamber and the apparatus of FIGURES 7A and 7B. The amount of H_2O_2 released from the PP at 175°C was greater than for SC and PO. Although SC released the least amount of H_2O_2 at 175°C, significantly more release was seen when the amount of sample was increased.

Table 17

RELEASE OF PEROXIDE IN 75 LITER CHAMBER

	SC	PO	PP
Temp. to release H_2O_2 (by DSC)	170°C	150°C	130°C
With 2 grams sample			
At 125°C	0.3 mg/L	0.8 mg/L	1.0 mg/L
At 150°C	1.2 mg/L	2.0 mg/L	1.5 mg/L
At 175°C	1.8 mg/L	2.5 mg/L	3.4 mg/L
With 3 grams sample			
At 175°C	2.3 mg/L		
With 4 grams sample			
At 175°C	2.9 mg/L		

REPLACEMENT SHEET
08 APR 1997

Example 18

Efficacy tests using SC, PO and PP

2×10^6 *B. subtilis* var. niger spores were inoculated on a SS blade. Three inoculated blades were first placed in the front, middle and back positions of a Spunguard wrapped 10"x 21"x 3.5" polyphenylene oxide tray. The wrapped tray was then placed in a 75 liter vacuum chamber having an initial vacuum pressure of 0.2 torr. A 5.5" peroxide disk was made by heat-sealing the SC, SO or PP inorganic peroxide powders between three layers of Spunguard and one layer of aluminum foil coated with polypropylene film. The peroxide was released by contacting the disk for 2 minutes with an aluminum plate which had been preheated to 175°C, followed by an additional diffusion time of 8 minutes for a total exposure time of 10 minutes. After treatment, the three blades were separately placed in Trypticase Soy Broth (TSB) at 32°C for 7 days and scored for bacterial growth. The results are summarized in Table 18.

Table 18

EFFICACY TEST RESULTS

Peroxide Complex	Weight of Complex	Peroxide Conc.	Sterility (+/all)
PP	2 grams	3.4 mg/l	0/3
PO	2 grams	2.5 mg/l	0/3
SC	2 grams	1.8 mg/l	1/3
SC	3 grams	2.3 mg/l	0/3
SC	4 grams	2.9 mg/l	0/3

As can be seen in the table, no growth of spores was observed with the exception of 2 g SC (1/3). However, when the amount of SC subjected to vaporization was increased to 3 grams, no bacterial growth was observed. These results underscore the efficacy of sterilization using inorganic hydrogen peroxide compound.

REPLACEMENT SHEET
08 APR 1997

REPLACEMENT SHEET
08 APR 1997

Inorganic hydrogen peroxide complexes can be readily incorporated into the sterilization procedures described hereinabove in connection with organic peroxide complexes. For example, inorganic complexes can be used in connection with a plasma sterilization method, or in connection with a self-sterilizing enclosure where peroxide is slowly released from the complex. Similarly, inorganic complexes can also be used in the sterilization of articles having narrow lumens, whereby a vessel containing the inorganic peroxide complex is connected to the lumen. In addition, pressure pulsing of the vapor released from inorganic peroxide complexes can be employed. Other examples of the use of inorganic complexes for sterilization will be apparent to one having ordinary skill in the art upon reference to the present specification.

WE CLAIM:

1. An apparatus for hydrogen peroxide sterilization of an article, comprising:

a container for holding the article to be sterilized at a pressure of less than 50 torr; and

a source of hydrogen peroxide vapor in fluid communication with said container, said source comprising an inorganic hydrogen peroxide complex at a temperature greater than 86°C, said source configured so that said vapor can contact said article to effect sterilization.

2. The apparatus of Claim 1, wherein said pressure is less than 20 torr.

3. The apparatus of Claim 1, wherein said pressure is less than 10 torr.

4. The apparatus of Claim 1, wherein said source is located within said container.

5. The apparatus of Claim 1, further comprising an enclosure disposed outside of said container in which said complex is located, and an inlet providing fluid communication betweeen said container and said enclosure, such that vapor released from said complex travels along said inlet and into said container to effect sterilization.

6. The apparatus of Claim 1, wherein said inorganic hydrogen peroxide complex is a complex of sodium carbonate, potassium pyrophosphate or potassium oxalate.

7. The apparatus of Claim 1, further comprising a heater located within said container, whereby said complex is placed on said heater and heated to facilitate the release of said vapor from said complex.

8. The apparatus of Claim 7, wherein said heater is heated prior to contacting with said complex.

9. The apparatus of Claim 1, further comprising a vacuum pump in fluid communication with said container for evacuating the container.

REPLACEMENT SHEET
08 APR 1997

* C L M S *

REPLACEMENT SHEET
08 APR 1997

10. The apparatus of Claim 1, further comprising an electrode adapated to generate a plasma around said article.

11. The apparatus of Claim 10, wherein said electrode is inside said container.

12. The apparatus of Claim 10, wherein said electrode is spaced apart from said container and is adapated to flow plasma generated thereby towards and around said article.

13. The apparatus of Claim 1, wherein said complex is in a solid phase.

14. A method for hydrogen peroxide vapor sterilization of an article, comprising:

placing said article into a container; and

contacting the article with a hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex by heating the complex at a rate of at least 5°C/minute to contact and sterilize the article.

15. The method of Claim 14, wherein the heating rate is at least 10°C/minute.

16. The method of Claim 14, wherein the heating rate is at least 50°C/minute.

17. The method of Claim 14, wherein the heating rate is at least 1000°C/minute.

18. The method of Claim 14, wherein the complex has less than 10% water.

19. The method of Claim 14, further comprising heating said complex to facilitate the release of said vapor from said complex.

20. The method of Claim 19, wherein the heating step comprises contacting said complex with a pre-heated heater.

21. The method of Claim 19, wherein said complex is heated to a temperature greater than 86°C.

REPLACEMENT SHEET
08 APR 1997

22. The method of Claim 14, further comprising evacuating the container before introducing said vapor into said container at a pressure of less than 50 torr.

23. The method of Claim 22, wherein said pressure is less than 20 torr.

24. The method of Claim 22, wherein said pressure is less than 10 torr.

25. The method of Claim 14, further comprising generating a plasma around said article after introducing said vapor into said container.

26. The method of Claim 25, wherein said plasma is generated inside the container.

27. The method of Claim 25, wherein said plasma is generated outside the container and flowed inside the container and around said article.

28. The method of Claim 14, wherein the contacting step comprises pressure pulsing of said vapor.

29. A method for hydrogen peroxide sterilization of an article, comprising:

placing the article in a enclosure containing an inorganic hydrogen peroxide complex;

sealing said enclosure; and

allowing said enclosure to stand at a temperature below 70°C for a time sufficient to release hydrogen peroxide vapor from said complex to effect sterilization of the article.

30. The method of Claim 29, wherein said enclosure is allowed to stand at a pressure less than atmospheric pressure.

31. The method of Claim 29, wherein said enclosure is allowed to stand at a temperature below about 40°C.

32. The method of Claim 29, wherein said enclosure is heated to a temperature greater than 23°C to facilitate release of said vapor.

33. The method of Claim 29, wherein said enclosure is selected from the group consisting of a pouch, a container, a chamber and a room.

REPLACEMENT SHEET

08 APR 1997

34. The method of Claim 29, wherein said hydrogen peroxide complex is in the form of a powder.

35. The method of Claim 29, wherein said hydrogen peroxide complex is in the form of a tablet.

36. The method of Claim 29, wherein said sealing step comprises sealing said enclosure with a gas permeable material.

37. The method of Claim 36, wherein said gas permeable material is selected from the group consisting of TYVEK™, CSR wrap, and paper.

38. A sealed enclosure containing a sterile product and an inorganic hydrogen peroxide complex capable of releasing hydrogen peroxide vapor.

39. A potassium pyrophosphate hydrogen peroxide complex.

40. A method for hydrogen peroxide vapor sterilization of an article, comprising:

placing said article into a container; and

contacting the article with a hydrogen peroxide vapor to contact and sterilize the article, said vapor being released from an inorganic hydrogen peroxide complex which does not decompose to release a hydrohalic acid.

41. A method for hydrogen peroxide sterilization of an article having an exterior and a narrow lumen therein, comprising:

connecting a vessel containing an inorganic peroxide complex to the lumen of the article;

placing the article within a container, whereby said vessel remains connected to the lumen;

reducing the pressure within said container; and

contacting the lumen of the article with hydrogen peroxide vapor released from said inorganic peroxide complex at a temperature less than 70°C.

VAPOR STERILIZATION USING INORGANIC HYDROGEN PEROXIDE COMPLEXES

Abstract of the Disclosure

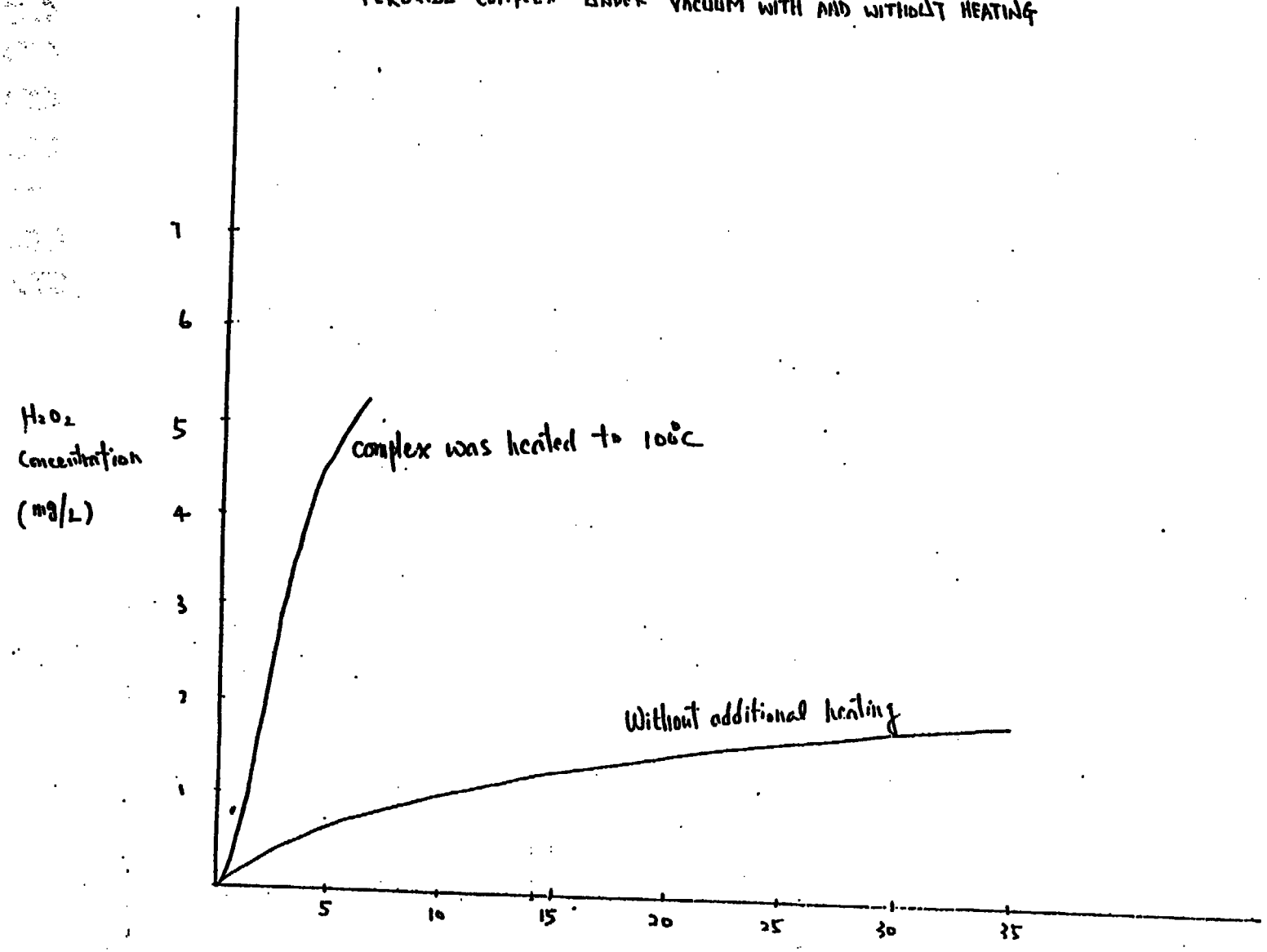
An apparatus and process for hydrogen peroxide vapor sterilization of medical instruments and similar devices make use of hydrogen peroxide vapor released from an inorganic hydrogen peroxide complex. The peroxide vapor can be released at room temperature and atmospheric pressure; however, the pressure used can be less than 50 torr and the temperature greater than 86°C to facilitate the release of hydrogen peroxide vapor. The heating rate can be greater than 5°C. Optionally, a plasma can be used in conjunction with the vapor.

Figure 1

REPLACEMENT SHEET

08 APR 1997

THE RELEASE OF HYDROGEN PEROXIDE FROM GLYCINE ANHYDRIDE PEROXIDE COMPLEX UNDER VACUUM WITH AND WITHOUT HEATING



REPLACEMENT SHEET
CO-8 AMD 1997