ANTI-ACNE METHOD AND COMPOSITION

ROBERT W. KLEIN, FORT WASHINGTON, PA; ALBERT M. PACKMAN, DRESHER, PA.

CONTINUING DATA

VERIFIED

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AND A CON OF 07/243,983 09/13/88 ABN
WHICH IS A CIP OF 07/061,951 07/27/97 ABN
WHICH IS A CON OF 06/806,627 12/12/85 ABN

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ANTI-ACNE METHOD AND COMPOSITION

U.S. DEPT. of COMM.-Pat. & TM Office-PTO-438L (rev. 10-78)

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Phyllis G. Spiavack
Assistant Examiner

Total Claims 10
Print Claim 1

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Amount Due $10,100.00
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FACE
**CONTINUING APPLICATION**

**FOREIGN/PCT APPLICATION**

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**PARTS OF APPLICATION FILED SEPARATELY**

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<th>PREPARED FOR ISSUE</th>
<th>CLAIMS ALLOWED</th>
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<tr>
<td>Assistant Examiner</td>
<td>Docket Clerk</td>
<td>Total Claims</td>
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- **Amount Due:**
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**DRAWING**

- **Sheets Drgw.:**
- **Figs. Drgw.:**
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- **Class:**
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**CONTINUING DATA**********************
VERIFIED THIS APPLN IS A CON OF 07/891,449 05/29/92
AND A CON OF 07/243,883 09/13/88 ABN

WHICH IS A CIP OF 07/061,951 07/27/87 ABN

WHICH IS A CON OF 06/808,627 12/12/85 ABN

**FOREIGN/PCT APPLICATIONS************
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ANTI-ACNE METHOD AND COMPOSITION

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By authority of the COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer
U.S. PATENT APPLICATION

Serial Number: 07/891,449  
Filing Date: 05/29/92  
Rule 60: 514  
Group Art Unit: 1205

Applicant: ROBERT W. KLEIN, FORT WASHINGTON, PA; ALBERT M. PACKMAN, DRESHER, PA.

**CONTINUING DATA***************
VERIFIED
THIS APPLN IS A CON OF 07/243,883 09/13/88
WHICH IS A CIP OF 07/061,951 07/27/87 ABN
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**FOREIGN/PCT APPLICATIONS***********
VERIFIED

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ANTI-ACNE METHOD AND COMPOSITION

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1. Application papers. 5-24-92
2. Res.
3. Res.
4. NOTICE OF ABANDONMENT 3-3-93
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Interview Summary

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ANTI-ACNE METHOD AND COMPOSITION

Inventors: Robert W. Klein, Fort Washington; Albert M. Packman, Dresher, both of Pa.


Filed: Apr. 8, 1994

Related U.S. Application Data


Field of Search

514/24, 5, 859, 43, 514/714

References Cited

U.S. PATENT DOCUMENTS

3,952,099 4/1976 Smith 514/859 X

3,969,516 7/1976 Stoughton 514/859 X

4,497,794 2/1985 Klein et al. 426/91

OTHER PUBLICATIONS


Primary Examiner—Marianne M. Cintins

Assistant Examiner—Phyllis G. Spivack

Attorney, Agent, or Firm—Ross J. Oehler

ABSTRACT

Composition and method for the treatment of acne including a peroxide and an antibiotic selected from the lincomycin family of antibiotics.

10 Claims, No Drawings
1

ANTI-ACNE METHOD AND COMPOSITION

This is a continuation of application Ser. No. 07/891,449 filed on May 29, 1992, abandoned and a continuation of Ser. No. 07/243,883, filed Sep. 13, 1988, abandoned, which is a continuation-in-part of Ser. No. 061,951, filed Jul. 27, 1987, abandoned, which is a continuation of Ser. No. 808,627, filed Dec. 12, 1985, abandoned.

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FIELD OF THE INVENTION

This invention relates to a method and pharmaceutical composition useful for the topical treatment of acne. Acne is a common inflammatory disease which is very common at puberty and which occurs in skin areas where sebaceous glands are largest, most numerous, and most active. In its more severe form, acne is a superficial disorder which is evidenced by slight, spotty irritations, can be treated satisfactorily by ordinary skin hygiene. However, pilosebaceous follicles occurs and results in the formation of pustules, infected cysts and, in extreme cases, canalizing inflamed and infected sacs, which may become extensive and leave permanent, disfiguring scars.

Therapeutic methods for treating acne include the systemic and topical administration of anti-acne agents such as antibiotics or derivatives of Vitamin A acid. In all but the severest of cases, systemic treatment of acne is not desirable because of side effects. However, systemic methods have been extensively to treat acne because there has not available a topical formulation which possesses the level of therapeutic effectiveness desirable to relieve the unseemly symptoms of the acne disease condition.

One aspect of the present invention relates to an improved topical anti-acne composition.

REPORTED DEVELOPMENTS

Topical anti-acne preparations include, for example, sulfur, resorcinol, salicylic acid, benzoyl peroxide, and/or antibiotics. Exemplary antibiotics incorporated in compositions are disclosed in U.S. Pat. No. 3,969,516 (lincomycin family); BR Publication No. 1,594,314 (erythromycin); and U.S. Pat. No. 3,992,099 (tetracycline). Compositions containing a peroxide are reported in U.S. Pat. Nos. 3,555,422; 4,005,611; 4,387,107, and British Patent No. 1,594,314 and U.S. Pat. No. 4,497,794. Antibiotic-containing compositions which also include anti-inflammatory steriods are disclosed in U.S. Pat. No. 4,132,781.

Attempts to improve the effectiveness of topical antibiotic compositions for use in the treatment of acne have taken a number of approaches. One approach is reported in U.S. Pat. Nos. 3,989,815; 3,988,816; 3,991,203; 4,122,170; 4,316,893; 4,444,762; and EP 27,286, which disclose skin-penetrating vehicle compositions that reportedly increase the transdermal absorption of any physiologically active substance, including antibiotics. However, not all penetrating agents in combination with antibiotics are effective for the treatment of acne. For example, the aforesaid '781 patent discloses that the use of a skin-penetrating vehicle results in an effective anti-acne composition with erythromycin, but not with tetracycline.

A further approach relates to the use of a composition which utilized two different active agents, such as erythromycin, Vitamin A acid or benzoyl peroxide.
The peroxide is present in the composition in an amount of about 1% to about 30 wt. %, and preferably about 2.5% to 15 wt. % based on the total weight of the composition. A most preferred amount of peroxide is about 5% to about 10 wt. %. The preferred peroxide should be of high purity. An exemplary material includes peroxide in an amount which is not less than about 98% of the stated concentration on the label. Raw material and in the form of finely divided crystalline particles, preferably, micronized particles having a mean average particle size of less than about 55 microns.

The antibiotic is present in the composition in an amount of about 0.01 to about 3 wt. percent. A preferred composition is in the form of an aqueous gel, and the most preferred composition is an aqueous alcoholic gel. However, liquid suspensions and emulsions, as well as creams, ointments and powders are acceptable.

The gelling agent used in the preferred composition of this invention may be selected both as to type and quantity to give products of various viscosities. A variety of gelling agents may be used for the present purpose. Preferred gelling agents are micro-crystaline cellulose, colloidal magnesium silicate, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and the so-called hydroxylated vinyl polymers, particularly, those disclosed in U.S. Pat. No. 2,798,053. Those hydroxylated vinyl polymers of special interest herein can be described generally as interpolymer prepared from a monomeric mixture comprising a mono-olefinic acrylic acid and about 0.1% to about 10% by weight of the other monomer in the monomeric mixture of polymer of an oligosaccharide having hydroxyl groups which are etherified with allyl groups, said oligosaccharide containing at least two alkly groups per oligosaccharide molecule. Commercially available interpolymers of this type are marketed under the trademark Carbopol®. These are described as being polymers of acrylic acid cross-linked with about 1% of a polyalkyl ether of sucrose having an average of about 5.8 alkyl groups for each sucrose molecule. These polymers have molecular weight in the order of magnitude of 1,000,000. Such polymers are available from the B.F. Goodrich Chemical Company and are sold under such trademarks as Carbopol®. Closely related copolymers, such as Carbopol® 1342 are also acceptable.

The amount of gelling agent included in the present preferred gel composition can range from about 0.1% to about 15% by weight and preferably from about 0.5% to about 3% by weight, based on the total weight of the composition. The composition of the present invention may include a surface active agent or dispersing agent for use in preparing uniformly the active ingredients. A preferred composition includes a second surface active agent. Such agents include the esters of polyols and sugars, the products of the condensation of ethylene oxide with fatty acids, fatty alcohols, long-chain alkylphenols, long-chain mercaptans, long chain amides, polymers of polyhydroxylated fatty alcohols and alkylglycosyl ethers which are included in an amount of from about 2% to about 6% by weight.

Another preferred embodiment of the composition of the present invention has a pH which is effective in stabilizing the antibiotic and peroxide ingredients over time. The effective stabilizing pH is about 4.6 to about 5.7, and the preferred stabilizing pH is about 5.2 to about 5.5. The most preferred pH is about 5.3.

A further preferred composition of the present invention includes a stabilizing agent which acts as an effective barrier to the possible degradative interaction of the peroxide and the antibiotic. The preferred stabilizing agent is dioctyl sodium sulfosuccinate, for example, an amount of about 0.1% to about 6% by weight, and preferably about 0.5% to about 3% by weight.

One type of preparation may comprise a two-component system, wherein one component comprises the antibiotic in stable form and the other component comprises the peroxide component. Another type of preparation comprises a composition in which the two active ingredients are stabilized as described hereinabove and may consist of lightly uncharged at temperatures conventionally employed for the storage of clindamycin or tetracycline solutions. Conventional pharmaceutical processes may be used in making up these common forms of medicinal, topical compositions. As mentioned above, a basic type of topical preparation comprises a mixture of powdered peroxide and antibiotic with an inert diluent. Such a preparation should be sparingly applied to the skin.

The following examples are illustrative of the present invention.

**EXAMPLE 1**

The following ingredients are mixed together to form a powder which may be dusted on the affected skin area, from one to four times a day.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyl peroxide</td>
<td>1-35</td>
</tr>
<tr>
<td>calcium phosphate</td>
<td>65-98.5</td>
</tr>
<tr>
<td>clindamycin hydrochloride</td>
<td>0.1-5</td>
</tr>
<tr>
<td>water</td>
<td>Q.S.-100</td>
</tr>
</tbody>
</table>

**EXAMPLE 2**

A liquid suspension of the present invention may be prepared by combining the following ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>Q.S.-100</td>
</tr>
</tbody>
</table>
A second container includes a solution of clindamycin hydrochloride (1% w/w of the total weight of the composition) in an appropriate solvent, preferably water or ethanol. The amount of solvent used comprises about 3 cc of solvent.

EXAMPLE 3

A lotion manufactured in a two component system may be prepared as follows. The following ingredients are mixed in a first container:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>stearyl alcohol (and) Ceteareth-20</td>
<td>5.5</td>
</tr>
<tr>
<td>cetyl alcohol</td>
<td>0.75</td>
</tr>
<tr>
<td>C12-15 alcohol benzoate</td>
<td>5</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.1</td>
</tr>
<tr>
<td>PEG-100 stearate</td>
<td>0.25</td>
</tr>
<tr>
<td>water, deionized or distilled</td>
<td>70.3</td>
</tr>
<tr>
<td>propylene glycol</td>
<td>3.0</td>
</tr>
<tr>
<td>benzyl peroxide</td>
<td>5.0</td>
</tr>
<tr>
<td>acetone</td>
<td>10.0</td>
</tr>
<tr>
<td>dioctyl sodium sulfate succinate</td>
<td>0.1</td>
</tr>
</tbody>
</table>

A second container includes a solution of clindamycin hydrochloride (1% w/w of the total weight of the composition) in an appropriate solvent, preferably water or ethanol. The amount of solvent used comprises about 3 cc of solvent.

EXAMPLE 4

A cream is manufactured as follows: The following ingredients are mixed in a first container:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>stearyl alcohol (and) Ceteareth-20</td>
<td>11</td>
</tr>
<tr>
<td>cetyl-eneeal alcohol</td>
<td>1.25</td>
</tr>
<tr>
<td>C12-15 alcohol benzoate</td>
<td>5</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.01</td>
</tr>
<tr>
<td>PEG-100 stearate</td>
<td>0.05</td>
</tr>
<tr>
<td>water, deionized or distilled</td>
<td>64</td>
</tr>
<tr>
<td>propylene glycol</td>
<td>3</td>
</tr>
<tr>
<td>benzyl peroxide</td>
<td>5</td>
</tr>
<tr>
<td>acetone</td>
<td>10</td>
</tr>
<tr>
<td>dioctyl sodium sulfate succinate</td>
<td>0.1</td>
</tr>
</tbody>
</table>

A second container includes a solution of clindamycin hydrochloride (2% w/w of the contents of the first container) in an amount of an appropriate solvent, preferably water or ethanol, such that 3 cc of the solution is prepared for each 20 grams of the composition in the first container.

EXAMPLE 5

A gel according to the present invention is prepared by combining the following ingredients in the first container:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>water, deionized or distilled</td>
<td>54.65</td>
</tr>
<tr>
<td>Veegum @ (R. T. Vanderbuilt Co.)</td>
<td>1.5</td>
</tr>
<tr>
<td>carboxy vinyl polymer (acid)</td>
<td>1</td>
</tr>
<tr>
<td>dioctyl sodium sulfate succinate</td>
<td>1</td>
</tr>
<tr>
<td>dioisopropylamine</td>
<td>0.75</td>
</tr>
<tr>
<td>ethyl alcohol, 200°</td>
<td>35.1</td>
</tr>
<tr>
<td>benzyl peroxide (microized)</td>
<td>5</td>
</tr>
</tbody>
</table>

Clindamycin phosphate (3% w/w of the total gel weight) is included in a second container.

EXAMPLE 6

A two-part suspension is prepared from the following ingredients:

<table>
<thead>
<tr>
<th>First Container</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>water, deionized or distilled</td>
<td>66.97</td>
</tr>
<tr>
<td>Veegum @ (R. T. Vanderbuilt Co.)</td>
<td>1.5</td>
</tr>
<tr>
<td>polyacrylic acid</td>
<td>0.25</td>
</tr>
<tr>
<td>dioctyl sodium sulfate succinate</td>
<td>1</td>
</tr>
<tr>
<td>dioisopropylamine</td>
<td>0.18</td>
</tr>
<tr>
<td>ethyl alcohol, 200°</td>
<td>25</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.1</td>
</tr>
<tr>
<td>benzyl peroxide (microized)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second Container</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>clindamycin hydrochloride</td>
<td>2% w/w based on the total composition</td>
</tr>
</tbody>
</table>

EXAMPLE 7

Lincomycin is substituted for clindamycin in the compositions of Examples 3 to 6.

EXAMPLE 8

In the composition of the above examples t-butyl peroctoate is substituted for benzoyl peroxide.

EXAMPLE 9

Tetracycline is substituted for clindamycin in the compositions of Examples 3 to 6.

EXAMPLE 10

Fifteen mg of Carbomer (15 mg) is added to distilled water (495 ml) while stirring. Stirring is continued for approximately 45 minutes. A solution of sodium hydroxide (4.09 mg) in distilled water (4.9 ml) is added and stirring is continued for 10 minutes. Ethyl alcohol (150 ml) and methyl salicylate (1 mg) are added to the stirred solution, followed by wet pack micronized benzoyl peroxide (50% benzoyl peroxide-50% water) (210 mg), and distilled water (80 ml). The resulting mixture is stirred until a smooth gel is obtained. A 20 g sample of the gel is mixed with a solution of clindamycin hydrochloride (800 mg) in distilled water (3 ml) affording a gel containing about 34.4 mg of clindamycin hydrochloride per gram of gel.
The following gel formulation including tetracycline is prepared according to the procedure described in Example 10.

Applicant has found that when compositions having different pH are subjected to accelerated decomposition conditions of 50°C, compositions having a pH below about 4.6 exhibit an unacceptable odor and evidence degradation of the peroxide. Similarly, compositions having a pH above about 5.7 show signs of clindamycin degradation. However, after 30 days, the composition having an initial pH of about 5.3 shows excellent stability. Neither peroxide nor clindamycin appear to degrade as measured by HPLC. The 30-day aged composition shows no evidence of peroxide decomposition and 90% of the clindamycin is retained in the composition.

The Composition of the present invention may be applied to the afflicted skin of an acne sufferer for a period of time on a regular basis such that the acne condition is brought under control.

A preferred regimen of treatment comprises the application of the composition from about one to about four times a day. The resultant product has good stability and is effective for use in the treatment of acne.

EXAMPLE 12

An aerosol spray according to the present invention may be prepared as follows. The following ingredients, in amounts within the below indicated ranges, are blended together and the resulting mixture charged into one chamber of a dual chamber aerosol container.

<table>
<thead>
<tr>
<th>W/W Percent</th>
<th>55 tyl sodium sulfocuccinate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzyl peroxide (microsized)</td>
<td>5.46</td>
</tr>
<tr>
<td>tetracycline</td>
<td>2</td>
</tr>
<tr>
<td>ethyl alcohol</td>
<td>20</td>
</tr>
<tr>
<td>PEG-8 caprate</td>
<td>6</td>
</tr>
<tr>
<td>colloidal magnesium aluminum silicate</td>
<td>2.5</td>
</tr>
<tr>
<td>hydroxyethylmethylcellulose</td>
<td>0.73</td>
</tr>
<tr>
<td>citric acid</td>
<td>0.03</td>
</tr>
<tr>
<td>dioctyl sodium sulfocuccinate</td>
<td>0.09</td>
</tr>
<tr>
<td>water</td>
<td>Q.S.</td>
</tr>
</tbody>
</table>

The resultant product has good stability and is effective for use in the treatment of acne.

EXAMPLE 13

Aqueous gel compositions of varying pH are prepared according to the following formulation:

<table>
<thead>
<tr>
<th>W/W Percent</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzyl peroxide</td>
<td>5</td>
</tr>
<tr>
<td>clindamycin phosphate</td>
<td>1</td>
</tr>
<tr>
<td>carbomer @ 940</td>
<td>1</td>
</tr>
<tr>
<td>sodium hydroxide to desired pH</td>
<td>---</td>
</tr>
</tbody>
</table>

Comparative studies have shown unexpectedly that pH is a significant factor in determining the stability of the composition of the present invention. The active ingredients included in the compositions having a pH within the range described above are physically and chemically more stable than the ingredients included in compositions having a pH outside the defined range. This work is discussed in more detail below.

EXAMPLE 14

Aqueous gel compositions of various pH are prepared according to the following formulating:

5,446,028

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-continued

water | Q.S.

Applicant has found that when compositions having different pH are subjected to accelerated decomposition conditions of 50°C, compositions having a pH below about 4.6 exhibit an unacceptable odor and evidence degradation of the peroxide. Similarly, compositions having a pH above about 5.7 show signs of clindamycin degradation. However, after 30 days, the composition having an initial pH of about 5.3 shows excellent stability. Neither peroxide nor clindamycin appear to degrade as measured by HPLC. The 30-day aged composition shows no evidence of peroxide decomposition and 90% of the clindamycin is retained in the composition. The composition of the present invention may be applied to the afflicted skin of an acne sufferer for a period of time on a regular basis such that the acne condition is brought under control. A preferred regimen of treatment comprises the application of the composition from about one to about four times a day.

I claim:

1. A composition for the topical treatment of acne comprising a peroxide and antibiotic of the lincomycin family, said composition being substantially stable at a temperature of 50°C. for a period of thirty (30) days.

2. The composition according to claim 1, wherein the antibiotic comprises clindamycin or a pharmaceutically acceptable salt or ester thereof.

3. The composition according to claim 2 having a pH of about 4.6 to about 5.7.

4. The composition according to claim 2 comprising about 1 to about 30 weight percent benzoyl peroxide and about 0.01 to about 5 weight percent clindamycin or a pharmaceutically acceptable salt or ester thereof.

5. A method for treating acne comprising topical administration to a patient afflicted with acne of an effective amount of the composition according to claim 1.

6. An aqueous gel composition for the topical treatment of acne comprising a peroxide, an antibiotic of the lincomycin family and a surfactant.

7. The aqueous gel composition according to claim 6, wherein the peroxide comprises benzoyl peroxide, the antibiotic comprises clindamycin and the surfactant comprises dioctyl sodium sulfocuccinate.

8. The composition according to claim 7 having a pH of about 4.6 to about 5.7.

9. The aqueous gel composition according to claim 7, comprising about 0.5 to about 3 weight percent of dioctyl sodium sulfocuccinate.

10. A method for treating acne comprising topical administration to a patient afflicted with acne of an effective amount of the composition according to claim 6.
Field of the Invention

This invention relates to a method and pharmaceutical composition useful for the topical treatment of acne.

Acne is a common inflammatory disease which is very common at puberty and which occurs in skin areas where sebaceous glands are largest, most numerous, and most active. In its milder forms, acne is a superficial disorder which is evidenced by slight, spotty irritations, and which can be treated satisfactorily by ordinary skin hygiene. However, pilosebaceous follicles occurs and results in the formation of pustules, infected cysts and, in extreme cases, canalizing inflamed and infected sacs, which may become extensive and leave permanent, disfiguring scars.

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Topical anti-acne preparations include, for example, sulfur, resorcinol, salicylic acid, benzoyl peroxide, and/or antibiotics. Exemplary antibiotics incorporated in compositions are disclosed in U.S. Pat. No. 3,969,516 (lincomycin family); BR Publication No. 1,594,314 (erythromycin); and U.S. Pat. No. 3,952,099 (tetracycline).

Compositions containing a peroxide are reported in U.S. Patent Nos. 3,535,422; 4,056,611; 4,387,107, and British Publication No. 1,594,314 and U.S. Pat. No. 4,497,794. Antibiotic-containing compositions which also include anti-inflammatory steroids are disclosed in U.S. Pat. No. 4,132,781.

Attempts to improve the effectiveness of topical antibiotic compositions for use in the treatment of acne have taken a number of approaches. One approach is reported in U.S. Pat. Nos. 3,989,815; 3,989,816; 3,991,203; 4,122,170; 4,316,893; 4,444,762; and EP 27,286, which disclose skin-penetrating vehicle compositions that reportedly increase the transdermal absorption of any physiologically active substance, including antibiotics. However, not all penetrating agents in combination with antibiotics are effective for the treatment of acne. For example, the aforesaid '781 patent discloses that the use of a skin-penetrating vehicle results in an effective anti-acne composition with erythromycin, but not with tetracycline.
A further approach relates to the use of a composition which utilized two different active agents, such as erythromycin, vitamin A acid or benzoyl peroxide. Compositions including mixtures of a peroxide and erythromycin are reported in British Publication No. 1,594,314 and U.S. Pat. No. 4,497,734.

The reported topical anti-acne methods and compositions exhibit the disadvantages of limited effectiveness and frequent excessive adverse skin reactions.

Summary of the Invention

This invention relates to a method for the treatment of acne comprising the topical administration, to a patient afflicted therewith, of a topically effective amount of a peroxide and an antibiotic from the lincomycin or tetracycline families.

As noted above, the prior art discloses compositions which include separately benzoyl peroxide or an antibiotic of the lincomycin or tetracycline family. Another aspect of the present invention relates to a composition which is effective in the treatment of acne, and which includes, as essential ingredients, a peroxide and an antibiotic from the lincomycin or tetracycline families or a pharmaceutically acceptable salt or ester thereof.

Another aspect of this invention is the provision of a stable anti-acne composition by adjusting the pH of the composition to an effective stabilizing pH and/or by incorporating an effective stabilizing amount of docusate salts, such as dioctyl sodium sulfosuccinate.

An advantage of the present invention relates to the surprising speedy onset of effectiveness.
These and other aspects of the present invention are described in more detail below.

**Detailed Description**

The term "antibiotic of the lincomycin family" is used herein to refer to a class of antibiotic substances originally recovered from *streptomyces lincolnensis*. Exemplary antibiotics include lincomycin and clindamycin and their pharmaceutically acceptable salts and esters such as their hydrochlorides and phosphates. Lincomycin is a derivative of the amino acid trans-L-4-α-propyl-hygrinic acid coupled to a derivative of an octose substituted by a methylmercaptyl group. Clindamycin is the 7-deoxy, 7-chloro derivative of lincomycin, and is otherwise known as methyl 7-chloro-6,7,8,трideoxy-6-[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-L-threo-α-D-galacto-octopyranoside. The lincomycin antibiotics are described in U.S. Pat. Nos. 3,475,407; 3,509,127; 3,544,551 and 3,513,155.

The term "antibiotic of the tetracycline family" is used herein to refer to a class of antibiotic substances originally recovered from *streptomyces aureofaciens*. Exemplary tetracyclines include chlortetracycline, oxytetracycline, tetracycline, demeclocycline, rolitetracycline, methacycline and doxycycline and their pharmaceutically acceptable salts such as acid addition salts, for example, their hydrochloride salts. Tetracycline, otherwise known as 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide, is described in U.S. Pat. Nos. 2,699,054; 2,712,517; 2,886,505; 3,005,023; 3,019,173; and 3,301,899. A review of tetracycline is published in "The Technology of the Tetracyclines," Vol. I. R.C. Evans, Ed. (Quadrangle Press, NY, 1968).
The term "peroxide" means an organic compound containing an oxygen-oxygen bond capable of cleaving and forming oxygen free-radicals. The peroxides include peroxyciids of carboxylic acids, peroxyesters of carboxylic acids and the dimeric product of carboxylic peroxyciids. Exemplary peroxides include t-butyl peroxyesters of straight and branched chain aliphatic carboxylic acids, and dimeric peroxides such as lauroyl peroxide and benzoyl peroxide. A preferred peroxide for use in the present invention is benzoyl peroxide, and the most preferred is microsized benzoyl peroxide.

The method of the present invention comprises the administration of an antibiotic of the lincomycin or tetracycline families to the skin of a patient suffering from acne either simultaneously with or shortly prior to or after the application of the peroxide. Accordingly, the two ingredients may be applied to the skin as a mixture or they may separately be applied to the skin. In the latter practice the antibiotic is applied first to the skin and immediately or shortly thereafter the peroxide in applied. Or, the order of application is reversed.

The composition of the present invention includes as essential ingredients benzoyl peroxide and an antibiotic from the lincomycin or tetracycline families, a preferred form of the composition comprising microsized benzoyl peroxide and clindamycin or tetracycline or a pharmaceutically acceptable salt or ester thereof. The most preferred composition includes clindamycin.

The peroxide is present in the composition in an amount of about 1% to about 30 wt.%, and preferably about 2.5% to 15 wt.% based on the total weight of the composition. A most preferred amount of peroxide is about 5 to
about 10 wt.%. The preferred peroxide should be of high purity. An exemplary material includes peroxide in an amount which is not less than about 98% of the stated concentration on the labeled raw material and in the form of finely divided crystalline particles, preferably, micronized particles having a mean average particle size of less than about 35 microns.

The antibiotic is present in the composition in an amount of about 0.01 to about 5 weight percent of the total composition, and preferably from about 0.1 to about 3 weight percent.

A preferred composition is in the form of an aqueous gel, and the most preferred composition is an aqueous alcoholic gel. However, liquid suspensions and emulsions, as well as creams, ointments and powders are acceptable.

The gelling agent used in the preferred composition of this invention may be selected both as to type and quantity to give products of various viscosities. A variety of gelling agents may be used for the present purposes. Preferred gelling agents are pure micro-crystalline cellulose, colloidal magnesium silicate, hydroxypropyl methyl cellulose and the so-called hydroxylated vinylic polymers, particularly, those disclosed in U.S. Patent No. 2,798,053. Those hydroxylated vinylic polymers of special interest herein can be described generally as interpolymer prepared from a monomeric mixture comprising a mono-olefinic acrylic acid and about 0.1% to about 10% by weight of the other monomers in the monomeric mixture of polyether of an oligosaccharide having hydroxyl groups which are etherified with allyl groups, said oligosaccharide containing at least two allyl groups per oligosaccharide molecule. Commercially available interpolymer of this type are marketed under the trade-mark Carbopols®. These are described as being polymers of acrylic acid cross-linked with about 1% of a polyalkyl
ether of sucrose having an average of about 5.8 alkyl groups for each sucrose molecule. These polymers have molecular weight in the order of magnitude of 1,000,000. Such polymers are available from the B.F. Goodrich Chemical Company and are sold under such trademarks as Carbopol® 940 and Carbopol® 941. Closely related copolymers, such as Carbopol® 1342 are also acceptable.

The amount of gelling agent included in the present preferred gel composition can range from about 0.1 to about 15% by weight, and preferably from about 0.5 to about 3% by weight, based on the total weight of the composition.

The composition of the present invention may include a surface active agent or dispersing agent to disperse uniformly the active ingredients. A preferred composition includes a second surface active agent. Such agents include the esters of polyols and sugars, the products of the condensation of ethylene oxide with fatty acids, fatty alcohols, long-chain alkyphenols, long-chain mercaptans, long chain amides, polyethers of polyhydroxylated fatty alcohols and alkylpolyglycol ethers which are included in an amount of from about 2% to about 6% by weight.

Another preferred embodiment of the composition of the present invention has a pH which is effective in stabilizing the antibiotic and peroxide ingredients over time. The effective stabilizing pH is about 4.6 to about 5.7, and the preferred stabilizing pH is about 5.2 to about 5.5. The most preferred pH is about 5.3.

A further preferred composition of the present invention includes a stabilizing agent which acts as an effective barrier to the possible degradative interaction of the peroxide and the antibiotic. The preferred stab-
ilizing agent is dioctyl sodium sulfosuccinate, for example, an amount of about 0.1 to about 6% by weight, and preferably about 0.5% to about 3% by weight.

One type of preparation may comprise a two-component system, wherein one component comprises the antibiotic in stable form and the other component comprises the peroxide component. Another type of preparation comprises a composition in which the two active ingredients are stabilized as described hereinabove and may coexist relatively unchanged at temperatures conventionally employed for the storage of clindamycin or tetracycline solutions. Conventional pharmaceutical processes may be used in making up these common forms of medicinal, topical compositions.

As mentioned above, a basic type of topical preparation comprises a mixture of powdered peroxide and antibiotic with an inert diluent. Such a preparation should be sparingly applied to the skin.

The following examples are illustrative of the present invention.

**Example 1**

The following ingredients are mixed together to form a powder which may be dusted on the affected skin area, from one to four times a day.

<table>
<thead>
<tr>
<th>W/W Percent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>benzoyl peroxide</strong></td>
<td>1 - 35</td>
</tr>
<tr>
<td><strong>calcium phosphate</strong></td>
<td>63 - 98.5</td>
</tr>
<tr>
<td><strong>clindamycin hydrochloride</strong></td>
<td>0.1 - 5</td>
</tr>
</tbody>
</table>

**Example 2**

A liquid suspension of the present invention may be prepared by combining the following ingredients.
Other preparations which are representative of the present invention include the following examples.

**Example 3**

A lotion manufactured in a two component system may be prepared as follows. The following ingredients are mixed in a first container.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>stearyl alcohol (and) Ceteareth-20</td>
<td>5.5</td>
</tr>
<tr>
<td>cetyl alcohol</td>
<td>0.75</td>
</tr>
<tr>
<td>C12-15 alcohols benzoate</td>
<td>5</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.1</td>
</tr>
<tr>
<td>PEG-100 stearate</td>
<td>0.25</td>
</tr>
<tr>
<td>water, deionized or distilled</td>
<td>70.3</td>
</tr>
<tr>
<td>propylene glycol</td>
<td>3.0</td>
</tr>
<tr>
<td>benzoyl peroxide</td>
<td>5.0</td>
</tr>
<tr>
<td>acetone</td>
<td>10.0</td>
</tr>
<tr>
<td>dioctyl sodium sulfosuccinate</td>
<td>0.1</td>
</tr>
</tbody>
</table>

A second container includes a solution of clindamycin hydrochloride (1% w/w of the total weight of the total composition) in an appropriate solvent, preferably water or ethanol. The amount of solvent used comprises an amount which dissolves about 2 grams of clindamycin HCl in about 3 cc of solvent.

Both containers may be put in a single marketable package with the instructions that the contents of the two containers be thoroughly mixed prior to the composition’s application to the skin. For each 3cc of solution in the second container, the first container contains about 20 grams of composition. An alternate method comprises the
stepwise application of the composition in the first container and the clindamycin solution in the second container so that the two-part composition is mixed on the skin.

Example 4

A cream is manufactured as follows:

The following ingredients are mixed in a first container:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>stearyl alcohol (and) Ceteareth-20</td>
<td>11</td>
</tr>
<tr>
<td>cetyl-stearyl alcohol</td>
<td>1.25</td>
</tr>
<tr>
<td>Cl2-15 alcohol benzoate</td>
<td>5</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.01</td>
</tr>
<tr>
<td>PEG-100 stearate</td>
<td>0.85</td>
</tr>
<tr>
<td>water, deionized or distilled</td>
<td>64</td>
</tr>
<tr>
<td>propylene glycol</td>
<td>3</td>
</tr>
<tr>
<td>benzoyl peroxide</td>
<td>5</td>
</tr>
<tr>
<td>acetone</td>
<td>10</td>
</tr>
<tr>
<td>dioctyl sodium sulfosuccinate</td>
<td>0.1</td>
</tr>
</tbody>
</table>

A second container includes a solution of clindamycin hydrochloride (2% w/w of the contents of the first container) in an amount of an appropriate solvent, preferably water or ethanol, such that 3cc of the solution is prepared for each 20 grams of the composition in the first container.
Example 5

A gel according to the present invention is prepared by combining the following ingredients in the first container.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>water, deionized or distilled</td>
<td>54.65</td>
</tr>
<tr>
<td>Veegum® (R.T. Vanderbuilt Co.)</td>
<td>1.5</td>
</tr>
<tr>
<td>carboxy vinyl polymer (acid)</td>
<td>1</td>
</tr>
<tr>
<td>dioctyl sodium sulfosuccinate</td>
<td>1</td>
</tr>
<tr>
<td>diisopropanolamine</td>
<td>0.75</td>
</tr>
<tr>
<td>ethyl alcohol, 200°</td>
<td>35.1</td>
</tr>
<tr>
<td>benzoyl peroxide (micronized)</td>
<td>5</td>
</tr>
</tbody>
</table>

Clindamycin phosphate (3% w/w of the total gel weight) is included in a second container.

Example 6

A two-part suspension is prepared from the following ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>water, deionized or distilled</td>
<td>66.97</td>
</tr>
<tr>
<td>Veegum® (R.T. Vanderbuilt Co.)</td>
<td>1.50</td>
</tr>
<tr>
<td>polyacrylic acid</td>
<td>0.25</td>
</tr>
<tr>
<td>dioctyl sodium sulfosuccinate</td>
<td>1</td>
</tr>
<tr>
<td>diisopropanolamine</td>
<td>0.18</td>
</tr>
<tr>
<td>ethyl alcohol, 200°</td>
<td>25</td>
</tr>
<tr>
<td>butylated hydroxyanisole</td>
<td>0.1</td>
</tr>
<tr>
<td>benzoyl peroxide (micronized)</td>
<td>5</td>
</tr>
</tbody>
</table>

Second Container

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>2% w/w based on the total composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>clindamycin hydrochloride</td>
<td></td>
</tr>
</tbody>
</table>

Example 7

Lincomycin is substituted for clindamycin in the compositions of Examples 3 to 6.
Example 8
In the composition of the above examples t-butyl peroctoate is substituted for benzoyl peroxide.

Example 9
Tetracycline is substituted for clindamycin in the compositions of Examples 3 to 6.

Example 10
Fifteen mg of Carbomer (15 mg) is added to distilled water (495 mg) while stirring. Stirring is continued for about 45 minutes. A solution of sodium hydroxide (4.09 mg) in distilled water (4.9 ml) is added and stirring continued for 10 minutes. Ethyl alcohol (150 ml) and methyl salicylate (1 mg) are added to the stirred solution, followed by wet pack micronized benzoyl peroxide (50% benzoyl peroxide - 50% water) (210 mg), and distilled water (80 ml). The resulting mixture is stirred until a smooth gel is obtained.

A 20 g sample of the gel is mixed with a solution of clindamycin hydrochloride (800 mg) in distilled water (3 ml) affording a gel containing about 34.4 mg of clindamycin hydrochloride per gram of gel.

Example 11
The following gel formulation including tetracycline is prepared according to the procedure described in Example 10.

<table>
<thead>
<tr>
<th>Component</th>
<th>W/W Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyl peroxide (microsized)</td>
<td>5.46</td>
</tr>
<tr>
<td>tetracycline</td>
<td>2</td>
</tr>
<tr>
<td>ethyl alcohol</td>
<td>20</td>
</tr>
<tr>
<td>PEG-8 caprate</td>
<td>6</td>
</tr>
<tr>
<td>colloidal magnesium aluminum silicate</td>
<td>2.5</td>
</tr>
<tr>
<td>hydroxyethylmethylcellulose</td>
<td>0.75</td>
</tr>
<tr>
<td>citric acid</td>
<td>0.05</td>
</tr>
</tbody>
</table>
The resultant product has good stability and is effective for use in the treatment of acne.

Example 12

An aerosol spray according to the present invention may be prepared as follows.

The following ingredients, in amounts within the below indicated ranges, are blended together and the resulting mixture charged into one chamber of a dual chamber aerosol container.

<table>
<thead>
<tr>
<th>W/W Percent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyl peroxide</td>
<td>1 - 20</td>
</tr>
<tr>
<td>calcium phosphate</td>
<td>65 - 97</td>
</tr>
<tr>
<td>calcium stearate</td>
<td>1 - 10</td>
</tr>
<tr>
<td>PPG-15 stearyl ether</td>
<td>0.5 - 5</td>
</tr>
</tbody>
</table>

Clindamycin phosphate (0.1-5wt%) is charged into the second chamber of the container and the container is pressurized with aerosol propellant.

Comparative studies have shown unexpectedly that pH is a significant factor in determining the stability of the composition of the present invention. The active ingredients included in the compositions having a pH within the range described above are physically and chemically more stable than the ingredients included in compositions having a pH outside the defined range. This work is discussed in more detail below.

Example 13

Aqueous gel compositions of varying pH are prepared according to the following formulation:

<table>
<thead>
<tr>
<th>W/W Percent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyl peroxide</td>
<td>5</td>
</tr>
</tbody>
</table>
Applicant has found that when compositions having different pH are subjected to accelerated decomposition conditions of 50°C, compositions having a pH below about 4.6 exhibit an unacceptable odor and evidence degradation of the peroxide. Similarly, compositions having a pH above about 5.7 show signs of clindamycin degradation. However, after 30 days, the composition having an initial pH of about 5.3 shows excellent stability. Neither peroxide nor clindamycin appear to degrade as measured by HPLC. The 30-day aged composition shows no evidence of peroxide decomposition and 90% of the clindamycin is retained in the composition.

The composition of the present invention may be applied to the afflicted skin of an acne sufferer for a period of time on a regular basis such that the acne condition is brought under control. A preferred regimen of treatment comprises the application of the composition from about one to about four times a day.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>clindamycin phosphate</td>
<td>1</td>
</tr>
<tr>
<td>carbomer 940</td>
<td>1</td>
</tr>
<tr>
<td>sodium hydroxide</td>
<td>to desired pH</td>
</tr>
<tr>
<td>water</td>
<td>QS</td>
</tr>
</tbody>
</table>
I claim:

1. A method for the treatment of acne comprising the topical administration to a patient afflicted with acne of a topically effective amount of a peroxide and an antibiotic of the lincomycin or the tetracycline families.

2. A method according to claim 1 wherein said peroxide is benzoyl peroxide.

3. A method according to claim 2 wherein said antibiotic is clindamycin or a pharmaceutically acceptable salt or ester thereof.

4. A method according to claim 3 wherein said peroxide and clindamycin are administered in the form of an aqueous gel composition.

5. A method according to claim 4 wherein said peroxide and clindamycin are administered sequentially to the skin of said patient.

6. A method according to claim 5 wherein said the pH of said composition is about 4.6 to about 5.7.

7. A composition for the topical treatment of acne comprising a peroxide and an antibiotic of the lincomycin or tetracycline families,

8. A composition according to claim 7, comprising clindamycin and/or a pharmaceutically acceptable salt thereof, and micronized benzoyl peroxide.

9. An aqueous composition according to claim 8 comprising about one to about 30 wt.% micronized benzoyl peroxide, about 0.01 to about 5 wt. percent clindamycin.
or a pharmaceutically acceptable salt or ester thereof, and having a pH of about 4.6 to about 5.7.

10. An aqueous gel composition for the treatment of acne comprising benzoyl peroxide, clindamycin or a pharmaceutically acceptable salt thereof, and a surfactant.

11. An aqueous gel composition according to claim 10 comprising:
   about 2.5 to about 15 wt.% micronized benzoyl peroxide;
   about 0.1 to about 3 wt.% clindamycin or a pharmaceutically acceptable salt or ester thereof; and
   about 0.1 to about 6 wt.% of a surfactant.

12. An aqueous gel composition according to claim 11 wherein said surfactant is dioctyl sodium sulfosuccinate.

13. A composition according to Claim 12 comprising about 0.5 to about 3 wt.% of said sulfosuccinate.

14. A composition according to Claim 13 comprising about 5 to about 10 wt.% of said peroxide.

15. A composition according to Claim 14 having a pH of about 4.6 to about 5.7.

16. A composition according to Claim 7 in the form of an aqueous gel comprising about 1 to about 30 wt.% of micronized benzoyl peroxide, about 0.01 to about 5 wt.% of tetracycline and about 0.1 to about 6 wt.% of a surfactant.

17. A composition according to Claim 16 wherein said surfactant is dioctyl sodium sulfosuccinate.
18. A composition according to Claim 17 comprising about 2.5 to about 15 wt.% of said peroxide, about 0.1 to about 3 wt.% of said tetracycline and about 0.5 to about 3 wt.% of said sulfosuccinate.

19. A composition according to Claim 18 comprising about 5 to about 10 wt.% of said peroxide.

20. A composition according to Claim 19 having a pH of about 4.6 to about 5.7.
Abstract of the Disclosure

5 Composition and method for the treatment of acne including a peroxide and an antibiotic selected from the lincomycin-or-tetracycline family of antibiotics.
As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one applicable item below)

- [x] original
- [ ] design

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application do not check any of next two items and check appropriate one of last three items.

- [ ] national stage of PCT
- [ ] supplemental

NOTE: If one of the following 3 items apply then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR CIP.

- [ ] divisional
- [ ] continuation
- [x] continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

ANTI-ACNE METHOD AND COMPOSITION

SPECIFICATION IDENTIFICATION

the specification of which: (complete (a), (b) or (c))

(a) [x] is attached hereto.

(b) [ ] was filed on ______________________________ as [ ] Serial No. ______________________________

or [ ] Express Mail No., as Serial No. not yet known ______________________________

and was amended on ______________________________

NOTE: Amendments filed after the original papers are deposited with the PTO which contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 CFR 1.67.

(Declaration and Power of Attorney [1-1]—page 1 of 4)
was described and claimed in PCT International Application No. filed on and as amended under PCT Article 19 on (if any).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations. § 1.56(a).

☐ In compliance with this duty there is attached an information disclosure statement, 37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor’s certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor’s certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

- (d) ☒ no such applications have been filed.

(e) ☐ such applications have been filed as follows

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>APPLICATION NUMBER</th>
<th>DATE OF FILING (month, day, year)</th>
<th>PRIORITY CLAIMED UNDER 37 USC 119</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐ YES ☐ NO</td>
</tr>
</tbody>
</table>

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

(Declaration and Power of Attorney [1-1]—page 2 of 4)
POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

Mr. James A. Nicholson
Reg. No. 25478

Alexis Barron, Esq.
Reg. No. 22702

Martin F. Savitzky, Esq.
Reg. No. 29699

SEND CORRESPONDENCE TO

Martin F. Savitzky, Esq.
Synnestvedt & Lechner
2600 One Reading Center
1101 Market Street
Philadelphia, PA 19107

DIRECT TELEPHONE CALLS TO:

Martin F. Savitzky, Esq.
(215) 923-4466 x313

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full name of sole or first inventor Robert W. Klein
Inventor's signature ________________
Date September 9, 1988 Country of Citizenship U.S.A.
Residence 310 Madison Avenue, Fort Washington, PA 19034
Post Office Address same

Full name of second joint inventor, if any Albert M. Packman
Inventor's signature ________________
Date September 9, 1988 Country of Citizenship U.S.A.
Residence 3223 Lenape Drive, Dresher, PA 19025
Post Office Address same

(Declaration and Power of Attorney [1-1]—page 3 of 4)
CHECK PROPER BOX(ES) IF ANY OF THE FOLLOWING ADDED PAGE(S) FORM A
PART OF THIS DECLARATION

☐ Signature for third and subsequent joint inventors. Number of pages added

☐ Signature by administrator/trix, executor/trix, or legal representative for de-
ceased or incapacitated inventor. Number of pages added

☐ Signature for inventor who refuses to sign or cannot be reached by person au-
thorized under 37 CFR 1.47. Number of pages added

☒ Added pages to combined declaration and power of attorney for divisional, con-
tinuation, or continuation-in-part (CIP) application.

☐ Number of pages added

☐ This declaration ends with this page

(Declaration and Power of Attorney [1-1]—page 4 of 4)
ADDED PAGE TO COMBINED DECLARATION AND POWER OF ATTORNEY
FOR DIVISIONAL, CONTINUATION OR CIP APPLICATION

(complete this part only if this is a divisional, continuation or CIP application)

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. 120

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

<table>
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<tr>
<th>PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 USC 120:</th>
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<tr>
<td><strong>U.S. APPLICATIONS</strong></td>
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<tr>
<td>1. 808,627</td>
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<td>2. 61,951</td>
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(Added Page to Combined Declaration and Power of Attorney for Divisional Continuation or CIP Application [1-2.1]—page 1 of 2)
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. 14,743-C USA

Anticipated Classification of this application:

Class Subclass

Prior application:
Examiner: L. Schenkmn
Art Unit: 125

Box Patent Application
Commissioner of Patents and Trademarks
Washington, D.C. 20231

TRANSMITTAL OF FILING UNDER 37 CFR 1.60(b)

WARNING: A c-i-p (continuation-in-part) cannot be filed under 37 CFR 1.60.

WARNING: Filing under 37 CFR 1.60 is permitted only if filed by the same or less than all the inventors named in the prior application.

WARNING: The filing of an application as the United States stage of an International Application requires an oath or declaration, 37 CFR 1.61(a)(4).

WARNING: The claims of this new application may be finally rejected in the first Office action where all claims of the new application are drawn to the same invention claimed in the earlier application and would have been properly finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. MPEP § 706.07(b).

This is a request for filing a

☐ Continuation

☐ Divisional

application under 37 CFR 1.60, of pending prior application

serial no. 0 7/ 243,883 filed on 9-13-88

date

of Robert W. Klein and Albert M. Packman

(inventor(s))

for ANTI-ACNE METHOD AND COMPOSITION

(title of invention)

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this 37 CFR 1.60 request and the documents referred to as attached therein are being deposited with the United States Postal Service on this date May 29, 1992 in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10, Mailing Label Number T8002596660US addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Joan Morris

(Type or print name of person mailing paper)

(Signature of person mailing paper)

NOTE: Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. (37 CFR 1.10(b)).
NOTE: 37 CFR 1.60 permits the omission of a declaration only if the prior application was complete as set forth in 37 CFR 1.51(a), namely, the prior application comprised at least (1) a specification, including a claim or claims; (2) a declaration; (3) drawings when necessary; and (4) the prescribed filing fee. Accordingly, as presently worded, 37 CFR 1.60 does not permit this procedure to be used where the prior application is pending but only the processing and retention fee required by 37 CFR 1.21(f) is paid or where the declaration was not filed.

1. Copy of Prior Application as Filed Which is Attached

NOTE: Under 37 CFR 1.60 practice signing and execution of the application by the applicant may be omitted provided the copy is supplied by and accompanied by a statement by the applicant or his or her attorney or agent that the application papers comprise a true copy of the prior application as filed and that no amendments referred to in the declaration filed to complete the prior application introduced new matter therein.

NOTE: This statement need not be verified if made by an attorney registered to practice before the PTO. (37 CFR 1.60(b)).

I hereby verify that the attached papers are a true copy of what is shown in my records to be the above identified prior application, including the oath or declaration originally filed (37 CFR 1.60).

The copy of the papers of prior application as filed which are attached are as follows:

- 14 page(s) of specification
- 3 page(s) of claims
- 1 page(s) of abstract
- [ ] sheet(s) of drawing

(Also complete part 6 below if drawings are to be transferred)

- 5 pages of declaration and power of attorney

If the copy of the declaration being filed does not show applicant’s signature indicate thereon that it was signed and complete the following:

[ ] in accordance with the indication required by 37 CFR 60(b) my records reflect that the original signed declaration showing applicant’s signature was filed on

[ ] the amendment referred to in the declaration filed to complete the prior application and I hereby state, in accordance with the requirements of 37 CFR 1.60(b), that this amendment did not introduce new matter therein.

2. Amendments

WARNING: “The claim of a new application may be finally rejected in the first Office action in those situations where (1) the new application is a continuing application of, or a substitute for, an earlier application, and (2) all the claims of the new application (a) are drawn to the same invention claimed in the earlier application, and (b) would have been properly finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application.” MPEP § 706.07(b).

[ ] Cancel in this application original claims ______________ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

[ ] A preliminary amendment is enclosed. (Claims added by this amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.)

NOTE: Only amendments reducing the number of claims or adding a reference to the prior application (Rule 1.78(a)) will be entered before calculating the filing fee and granting the filing date. 37 CFR 1.60(b).

NOTE: "When filing under Rule 1.60 retain at least one original claim from the patent application to assure a complete application." Notice of March 3, 1986 (1064 O.G. 37-29).

(37 CFR 1.60(b) [4-3]—page 2 of 8)
3. Petition for Suspension of Prosecution for the Time Necessary to File an Amendment

NOTE: Where it is possible that the claims on file will give rise to a first action final for this continuation application and for some reason an amendment cannot be filed promptly (e.g., experimental data is being gathered) it may be desirable to file a petition for suspension of prosecution for the time necessary.

☐ There is provided herewith a Petition To Suspend Prosecution For The Time Necessary to File An Amendment (New Application Filed Concurrently).

4. Fee Calculation (37 CFR 1.16)

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<td>Multiple dependent claim(s), if any (37 CFR 1.16(d))</td>
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<td></td>
<td>$220.00</td>
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</tbody>
</table>

☐ Fee for extra claims is not being paid at this time. (37 CFR 1.16(d))

NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the PTOL in any notice of fee deficiency. 37 CFR 1.16(d).

Filing Fee Calculation $690.00

5. Small Entity Status

☐ A verified statement that this filing is by a small entity:

☐ is attached

☐ has been filed in the parent application and such status is still proper and desired (37 CFR 1.28(a))

Filing Fee Calculation (50% of above) $ __

NOTE: Any excess of the full fee paid will be refunded if a verified statement is filed within 2 months of the date of timely payment of a full fee then the excess fee paid will be refunded on request. 37 CFR 1.28(a).

NOTE: 37 CFR 1.28(a), last sentence states: “Applications filed under 51.60 or 51.62 of this part must include a reference to a verified statement in a parent application if status as a small entity is still proper and desired.”

6. Drawings

WARNING: Do not check the following box if prior case is not to be abandoned.

☐ Transfer the drawings from the prior application to this application and, subject to item 17 below, abandon said prior application as of the filing date accorded this application. A duplicate copy of this request is enclosed for filing in the prior application file. (May only be used if signed by (1) applicant, (2) assignee of record or (3) attorney or agent of record authorized by 37 CFR 1.138 and before payment of issue fee.)

NOTE: "A registered attorney or agent acting under the provisions of § 1.34(a), or of record, may also expressl abandon a prior application as of the filing date granted to a continuing application when filing such a continuing application." 37 CFR 1.138.

(37 CFR 1.60(b) [4-3]—page 3 of 8)
Transfer the following sheet(s) of drawing from the prior application to this application.

NOTE: Transferred sheets must be cancelled in prior application. 37 CFR 1.88.

☐ A copy of the amendment cancelling these sheets of drawing in the prior application is attached

☐ New drawings are enclosed

☐ formal

☐ informal

WARNING: DO NOT submit original drawings. A high quality copy of drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards of § 1.84. If corrections to the drawings are necessary, they should be made to the original drawings and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. Comments on proposed new 37 CFR 1.84. Notice of March 8, 1988 (1090 O.G. 57-62).

NOTE: "Identifying indicia such as the serial number, group art unit, title of the inventor, attorney's docket number, inventor's name, number of sheets, etc. not to exceed 2 1/4 inches (7.0 cm.) in width may be placed in a centered location between the side edges within three fourths inch (19.1 mm.) of the top edge. Either this marking technique on the front of the drawing or the placement, although not preferred, of this information and the title of the invention on the back of the drawings is acceptable." Proposed 37 CFR 1.84(1). Notice of March 9, 1988 (1090 O.G. 57-62).


☐ Priority of application serial no. 0 filed on is claimed under 35 U.S.C. 119.

☐ The certified copy has been filed in prior U.S. application serial no. on

☐ The certified copy will follow.


X Amend the specification by inserting before the first line the sentence:

"This is a

☐ continuation

☐ divisional

of copending application( )

Serial number 07/243,883 filed on 9-13-88 which is a continuation-in-part of Serial No. 61,951 filed on July 27, 1987, which is a continuation of Serial No. 808,627, filed on December 12, 1985.

International Application filed on which designated the U.S."
9. Inventorship Statement

NOTE: If the continuation or divisional application is filed by less than all the inventors named in the prior application a statement must accompany the application when filed requesting deletion of the names of the person or persons who are not inventors of the invention being claimed in the continuation or divisional application. 37 CFR 1.60(b) (emphasis added).

(a) With respect to the prior copending U.S. application from which this application claims benefit under 35 USC 120 the inventor(s) in this application is (are):

(complete applicable item below)

☐ the same

☐ less than those named in the prior application and it is requested that the following inventor(s) identified above for the prior application be deleted:

(Type name(s) of inventor(s) to be deleted)

(b) The inventorship for all the claims in this application are

☐ the same

☐ not the same, and an explanation, including the ownership of the various claims at the time the last claimed invention was made, is submitted.

10. Assignment

☐ The prior application is assigned of record to

☐ an assignment of the invention to __________________________________________

is attached. A separate "ASSIGNMENT COVER LETTER ACCOMPANYING NEW PATENT APPLICATION" is also attached.

NOTE: "If an assignment is submitted with a new application, send two separate letters - one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

11. Fee Payment Being Made At This Time

☐ Not Enclosed

☐ No filing fee is submitted. (This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently).

☒ Enclosed

☐ basic filing fee $ 690.00

☐ recording assignment ($40.00; 37 CFR 1.21(h)) $____________

☐ processing and retention fee ($130.00; 37 CFR 1.53(d) and 1.21(i)) $____________

(37 CFR 1.60(b) [4-3]—page 5 of 8)
NOTE: 37 CFR 1.21(1) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78 indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or else the processing and retention fee of § 1.21(1) must be paid within 1 year from notification under § 53(d).

Total fees enclosed $ 690.00

12. Method of Payment of Fees

☐ enclosed is a check in the amount of $ 690.00

☐ charge Account No. ____________ in the amount of ____________

A duplicate of this request is attached.

NOTE: Fees should be itemized in such a manner that is clear for which purpose the fees are paid. 37 CFR 1.22(b).

13. Authorization To Charge Additional Fees

WARNING: If no fees are being paid on filing do not complete this item.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claim charges are authorized.

☐ The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of the application to Account No. ____________

☐ 37 CFR 1.16(a), (f) or (g) (filing fees)

☐ 37 CFR 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)) it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☐ 37 CFR 1.17 (application processing fees)

WARNING: While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under § 1.136(a) this authorization should be made only with the knowledge that: “Submission of the appropriate extension fee under 37 CFR 1.136(a) is to no avail unless a request or petition for extension is filed.” [emphasis added]. Notice of November 5, 1985 (1060 O.G. 27).

☐ 37 CFR 1.18 (issue fee at or before mailing Notice of Allowance, pursuant to 37 CFR 1.311(b)).

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).

NOTE: 37 CFR 1.28(b) requires “Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying or at the time of paying . . . issue fee.” From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as “other than a small entity” and (b) no notification is required if the change is to another small entity.

14. Power of Attorney

☐ The power of attorney in the prior application is to

Alexis Barron

Attorney

Reg. No. 22,702

a. ☐ The power appears in the original papers in the prior application.
b. □ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. □ A new power has been executed and is attached.

d. □ Address all future communications to

(Item d may only be completed by applicant, or attorney or agent of record)

15. Maintenance of Copendency of Prior Application

(This item must be completed and the papers filed in the prior application if the period set in the prior application has run)

□ A petition, fee and response has been filed to extend the term in the pending prior application until _______________________.

NOTE: The PTO finds it useful if a copy of the petition filed in the prior application extending the term for response is filed with the papers constituting the filing of the Continuation Application. Notice of November 5, 1985 (1060 O.G. 27).

□ A copy of the petition for extension of time in the prior application is attached.

16. Conditional Petition for Extension of Time in Prior Application

(complete this item and file conditional petition in the prior application if previous item not applicable)

□ a conditional petition for extension of time is being filed in the pending parent application.

NOTE: The PTO finds it useful if a copy of the petition filed in the prior application extending the term for response is filed with the papers constituting the filing of the continuation application. Notice of November 5, 1985 (1060 O.G. 27).

□ A copy of the conditional petition for extension of time in the prior application is attached.

17. Abandonment of Prior Application (if applicable)

WARNING: (Do not complete this item if the application being filed is a divisional of the prior application which is not being abandoned)

NOTE: "A registered attorney or agent acting under the provisions of § 1.34(a), or of record, may also expressly abandon a prior application as of the filing date granted to a continuing application when filing such a continuing application." 37 CFR 1.138.

□ Please abandon the prior application at a time while the prior application is pending or when the petition for extension of time or to revive in that application is granted and when this application is granted a filing date so as to make this application copending with said prior application.

18. Notification in Parent Application of the Filing of This Confirmation Application
A notification of the filing of this confirmation is being filed in the parent application from which this application claims priority under 35 USC § 120.

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

May 29, 1992

Date

Alexis Barron, Esquire

Signature

P.O. Address of Signatory

1101 Market St., Suite 2600

Philadelphia, PA 19107

Tel. No.: (215) 923-4466

Reg. No. 22,702

(Complete the following if applicable)

Type name of assignee

Address of assignee

Title of person authorized to sign on behalf of assignee

Assignment recorded in PTO on

Reel Frame

(37 CFR 1.60(b) [4-3]—page 8 of 8)
This application has been examined. This action is made final.

A shortened statutory period for response to this action is set to expire 3 months from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133.

Part I

1. Notice of References Cited by Examiner, PTO-892.
5. Information on How to Effect Drawing Changes, PTO-1474.

Part II

SUMMARY OF ACTION

1. Claims 1-20 are pending in the application. Of the above, claims 1-20 are withdrawn from consideration.

2. Claims have been cancelled.

3. Claims are allowed.

4. Claims 1-20 are rejected.

5. Claims are objected to.

6. Claims are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on . Under 37 C.F.R. 1.84 these drawings are approved by the examiner.

10. The proposed additional or substitute sheet(s) of drawings, filed on has (have) been approved by the examiner.

11. The proposed drawing correction, filed on has been approved. disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has been received not been received.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other
The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 to 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Klein et al in view of Stoughton, Smith and Merck Index.

Klein et al teach anti-acne gel preparation containing an antibiotic, sodium sulfosuccinate and a peroxide. Stoughton and Smith teach the claimed antibiotics used in the treatment of acne. One skilled in the art would be motivated to substitute same for the antibiotics or the primary reference in view of their taught common utilities. Further, the use of lincomycin salts rather than the base compound in the instant composition is rendered obvious by Merck Index which teaches greater stability of the salt form.

Claims 1-20 are rejected on the grounds of Res Judicata in
view of the Board of Appeals decision in parent application SN 243,883.

Any inquiry concerning this communication should be directed to examiner Schenkman at telephone number (703) 308-1235.

Schenkman: lb
August 04, 1992

Leonard Schenkman
EXAMINER
ART UNIT 125
**NOTICE OF REFERENCES CITED**

### U.S. PATENT DOCUMENTS

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### FOREIGN PATENT DOCUMENTS

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### OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

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THE MERCK INDEX, 10th ed., 945328 (1983)
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*A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a.).*
NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant’s failure to respond to the Office letter, mailed 8/10/98.
2. ☐ Applicant’s letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant’s failure to timely file the response received within the period set in the Office letter.
4. ☐ Applicant’s failure to pay the required issue fee within the statutory period of 3 months from the mailing date of the Notice of Allowance.
   □ The issue fee was received on 11/10/98.
   □ The issue fee has not been received in Allowed Files Branch as of 11/10/98.

In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Deigar Inc. v. Schuyler, 172 U.S.P.Q. 513.

5. ☐ Applicant’s failure to timely correct the drawings and/or submit new or substitute formal drawings by 12/10/98 as required in the last Office action.
   □ The corrected and/or substitute drawings were received on 12/10/98.
6. ☐ The reason(s) below.

Examined

LEONARD SCHENKMAN
EXAMINER
MIT UNIT 125
Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

The holding of Abandonment mailed \text{Mar. 3/93} has been withdrawn.

The application has been returned to pending status.

The error is regretted.

\[Signature\]
February 10, 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Robert W. Klein and Albert M. Packman
Serial No. 07/891,449
Filed May 29, 1992
ANTI-ACNE METHOD AND COMPOSITION

Examiner L. Schenkman
Art Unit 1205

Attorney Docket No. 14,743-C USA

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, DC 20231, on February 10, 1993.

Alexis Barron

Petition for Extension of Time Under 37 CFR 1.136(a)

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

It is hereby requested that the term to respond to the Examiner’s Action of August 10, 1992 be extended three months from November 10, 1992 to February 10, 1993.

A check to cover the fee for the extension is enclosed. If there is any error in the fee submitted, please charge or credit the difference to Deposit Account No. 19-5425. A duplicate of this Petition is attached.

Respectfully submitted,

SYNNESTVEDT & LECHNER

Alexis Barron (Registration No. 22,702)

AB:jrm
Enclosure
February 10, 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Robert W. Klein and Albert M. Packman
Serial No. 07/891,449
Examiner L. Schenkman
Filed May 29, 1992
Group Art Unit 185
ANTI-ACNE METHOD AND COMPOSITION
Attorney Docket no. 14,743-C USA

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, DC 20231, on February 10, 1993.

Alexis Barron

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Examiner's Action of August 10, 1992, applicants amend as follows.

In the Claims

Cancel Claims 1 to 20 inclusive.

Please add the following claims.

21. An aqueous gel composition for the topical treatment of acne comprising:
about 2.5 to about 15 wt.% micronized benzoyl peroxide;
about 0.1 to about 3 wt.% clindamycin or a pharmaceutically acceptable salt or ester thereof;
and
about 0.1 to about 6 wt.% of a surfactant;
said composition having a pH of about 4.6 to about 5.7; and
said composition having stability characteristics such that, upon being subjected to a temperature of 50°C for a period of 30 days, the composition shows no evidence of decomposition of said peroxide and contains at least about 90 wt.% of said clindamycin or salt thereof.

22. A composition according to Claim 21 having a pH of about 5.3.

23. A method for the treatment of acne comprising the topical administration to a patient afflicted with acne of a topically effective amount of a composition according to Claim 21.

24. A method for the treatment of acne comprising the topical administration to a patient afflicted with acne of a
Remarks

The claims have been rejected under 35 USC §103 as being unpatentable over the disclosure of U.S. Patent No. 4,497,794 to Klein et al in view of the disclosure of U.S. Patent No. 3,969,516 to Stoughton, U.S. Patent No. 3,952,099 to Smith and the Merck Index. In addition, a res judicata rejection has been asserted against the claims.

Reconsideration is requested respectfully.

Summary of the Invention

All of the originally-file claims have been canceled in favor of added Claims 21 to 24 which include generic Claim 21. This claim is directed to an aqueous gel composition which is effective in treating acne and which comprises clindamycin or a salt thereof, micronized benzoyl peroxide, and a surfactant, each of the aforementioned being present in the proportions recited in Claim 21.

A critical aspect of the present invention is applicants’
finding that the peroxide/clindamycin composition should have a pH of about 4.6 to about 5.7 for purposes of stability. This is discussed in the third complete paragraph on page 7 of the application and in more detail in the first complete paragraph on page 14 of the present application.

Claim 21 recites explicitly that the stability properties of the composition are such that, when the composition is subjected to a temperature of 50°C (which represents accelerated decomposition conditions), the composition shows no evidence of peroxide decomposition and 90% of the clindamycin is retained in the composition. As set forth in the application on page 14, lines 5 to 10, a composition having a pH below about 4.6 exhibits an unacceptable odor and evidences degradation of the peroxide, and a composition having a pH of above about 5.7 shows signs of clindamycin degradation.

From the discussion which appears hereinbelow, it will be seen that none of the art of record discloses or in any way suggests a peroxide/clindamycin composition having a pH of about 4.6 to about 5.7 or the nature of the stability characteristics thereof.
Summary of the References

There is no reference in the Klein et al patent, the primary reference, to clindamycin and there is no reference in the patent to pH. This patent discloses an anti-acne composition containing peroxide and the antibiotic erythromycin. (Robert W. Klein is an inventor who is named on the primary reference and on the present application, with the Klein et al patent and the present application being assigned to the same entity.) The patent discloses that the addition of dioctyl sodium sulfosuccinate to an aqueous alcoholic gel comprising a peroxide and an erythromycin compound results in a composition which is stable with respect to the peroxide constituent and which provides stability to the composition (see respectively Column 3, lines 5-12 and Column 4, lines 23-26 of the Klein et al patent). The patent further discloses that erythromycin rapidly degrades in solution, even at room temperature, with refrigeration somewhat extending the shelf life of the solution (see the paragraph bridging Columns 3 and 4 of the patent and the subsequent two paragraphs).

The Stoughton patent discloses an anti-acne composition containing an antibiotic of the lincomycin family, of which clindamycin is a member. There is no reference in the patent to the stability or instability of the compositions described
therein. And, there is no reference in the patent to peroxide or pH.

The Smith patent discloses an anti-acne composition comprising tetracycline. There is no reference in this patent to clindamycin or a compound of the lincomycin family. The Smith patent refers to the instability of solutions of tetracycline hydrochloride. Smith suggests that this constituent be packaged separately from its solvent in order to avoid the instability problem (see the paragraph bridging Columns 22 and 23). There is no reference in the Smith patent to pH.

The Merck Index reference relates to lincomycin and discloses that it is more stable in its salt form. The disclosure does not identify what is meant by stability or instability, that is, the conditions under which instability may be encountered, and there is no disclosure concerning pH or benzoyl peroxide.

Discussion of the Section 103 Rejection

In the first instance, the provision of an anti-acne composition according to the combined disclosures of the references does not result in a composition which is the
subject of appellants' claims. As mentioned above, each of applicants' claims defines a composition which has a pH of about 4.6 to about 5.7. There are no references in the involved patents to pH.

Furthermore, there is of record in the present application a significant amount of information which constitutes solid evidence that the Klein et al composition and applicants' composition are significantly different. Such evidence relates to differences in stability of the compositions.

The Examiner's attention is directed to attached Exhibit A which consists of a verified copy of "Declaration of Robert W. Klein Under 37 CFR 1.132", the original of which was filed in applicants' patent application Serial No. 07/243,883. The Klein Declaration sets forth that the erythromycin component of a composition of the type disclosed in the Klein et al patent is unstable in the composition to the extent that 60% of the erythromycin destabilizes within a four-week period. The Klein Declaration further points out that the stability of erythromycin in the involved composition is not significantly pH dependent (see paragraph (5) of the Klein Declaration).

It is significant to note that the information in the
Klein Declaration is not inconsistent with the disclosure of the Klein et al patent which itself refers to the instability of erythromycin and which teaches the use for commercial applications of packages of ingredients, one package containing erythromycin only and the other package containing the remaining ingredients of the composition (see Column 4, lines 14 to 27 of the Klein et al patent).

There is absolutely no information in the Klein et al patent which has anything whatsoever to do with improving the stability of the compositions described therein by pH adjustment - such lack of reference to pH being consistent with the Klein Declaration which states explicitly that the stability of erythromycin in compositions of the types disclosed in the Klein et al patent is not significantly pH dependent.

In contrast however, the Klein Declaration includes information which indicates that the stability of lincomycin in compositions of the type described in the present application is strongly pH dependent (see paragraph (6) of the Klein Declaration and see also page 14 of the present application, first complete paragraph, which is repeated hereinabove on page 3). In addition, the Klein Declaration includes information which shows the excellent stability of a
composition of the type set forth in the present application (see paragraph (7) of the Klein Declaration and Exhibit A. thereof).

In summary, the information of record shows that an inventor of the primary reference and his assignee's literature acknowledge and show that compositions of the type disclosed in the primary reference are relatively unstable, whereas compositions of the type set forth in the claims of the present application are significantly more stable (the erythromycin of the Klein et al composition degrading to the extent of 60% after 4 weeks and the clindamycin constituent of the composition of the present application degrading to an extent of only 11.1% after 23 weeks). There is nothing in the prior art which indicates that such stable compositions can be realized by maintaining the pH of the composition within the range set forth in each of applicants' claims or that such composition would possess the stability properties recited in applicants' claims.

In view of the above, it is submitted that Claims 21 to 24 are patentable over the references cited by the Examiner.
The *Res Judicata* rejection

It is submitted respectfully that the Examiner's *res judicata* rejection has been overcome by the cancellation of claims which were considered by the Board of Appeals in applicants' parent application Serial No. 243,883 and by the presentation of Claims 21 to 24 which include recitations not recited in claims considered by the Board. Such recitations include the stability characteristics of the claimed composition.

A Petition for an extension of time is enclosed herewith.

An early and favorable action is requested respectfully.

Respectfully submitted,

SYNNESTVEDT & LECHNER

Alexis Barron  
(Registration No. 22,702)
February 10, 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re\ Application of Robert W. Klein
and Albert M. Packman
Serial No. 07/891,449
Filed May 29, 1992
ANTI-ACNE METHOD AND COMPOSITION
(Atty. Docket No. 14,743-C USA)

Verification

I hereby verify that the attached "Declaration of Robert W. Klein Under 37 CFR 1.132", dated June 8, 1990, filed June 11, 1990 in applicants' parent application Serial No. 07/243,883, is a true copy of what is shown in my records to be said Declaration.

Date

Exhibit A
June 8, 1990

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of
Robert W. Klein and Albert M. Packman
Serial No. 07/243,883

Filed on September 13, 1988

ANTI-ACNE METHOD AND COMPOSITION

Atty Docket No. 14,743-B USA

DECLARATION OF ROBERT W. KLEIN UNDER 37 CFR 1.132

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

Robert W. Klein hereby declares that:

(1) He was awarded the degree of Bachelor of Science by Hunter College in 1962.

(2) He is employed presently by Rorer Group Inc. (hereinafter "Rorèr") and has been employed by Rorer or a predecessor of Rorer since 1963. He currently holds the title of Manager of Product Development of Dermik Laboratories, Inc., (hereinafter "Dermik"), a subsidiary of Rorer and assignee of both the above-identified application and U.S. Patent No. 4,497,794 (hereinafter the "'794 patent"), the primary reference cited in the Office Action of November 22, 1989.

(3) He is a named inventor on both the present application and the '794 patent.
His responsibilities at Dermik include the development of skin care formulations and the coordination and supervision of tests for evaluating the stability of skin care formulations. As a result of his work at Dermik, he is familiar with the tendency of compositions within the scope of the present application and within the scope of the '794 patent to resist chemical change. He knows that compositions of the type described in the '794 patent tend to be unstable at room temperature whereas compositions of the type described in the present application are stable.

As to the instability of compositions of the type described in the '794 patent, reference is made to attached Exhibit A, which is entitled "I. Stability: Room Temperature Degradation Profile" and which relates to the instability of BENZAMYCIN® topical gel. This gel is an anti-acne formulation which contains erythromycin and is the type of composition described in the '794 patent. Exhibit A is a product information sheet for prescribing physicians and pharmacists. The assay referred to Exhibit A was conducted on behalf of Dermik by the microbiology unit of Rorer Group, Inc.

The above-mentioned assay examines the degradation profile of the erythromycin component of BENZAMYCIN® (3% erythromycin, 5% benzoyl peroxide) topical gel during room temperature (about 25°C) storage, and followed standard published microbiological methodology. The results of this assay are summarized below.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Erythromycin</th>
<th>% Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>3.00</td>
<td>-</td>
</tr>
<tr>
<td>1 Week</td>
<td>2.76</td>
<td>8</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>2.10</td>
<td>30</td>
</tr>
<tr>
<td>3 Weeks</td>
<td>1.74</td>
<td>42</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>1.20</td>
<td>60</td>
</tr>
</tbody>
</table>

Because of such instability at room temperature, Dermik recommends that BENZAMYCIN® topical gel be kept refrigerated.
The stability of erythromycin in BENZAMYCIN® topical gel at room temperature is not significantly pH dependent. BENZAMYCIN® topical gel has a pH of about 5.6.

(6) The room temperature stability of lincomycin in formulations of the present invention is strongly pH dependent, with excellent stability at a pH from 4.6 to 5.7.

(7) Exhibit B, attached hereto, consists of a copy of page 31 of a validation report for the assay of clindamycin in formulations of the type described in the present application. This assay examined the amount of clindamycin remaining in formulations which had been stored at room temperature, and followed standard published microbiological methodology. After 23 weeks of storage, the clindamycin concentration in the formulations fell by a range from 2.67% to 18.51%, with an average degradation of 11.1%, an excellent showing of room temperature stability.

(8) In view of the poor room temperature stability of the formulations of the type described in the '794 patent, he believes that the excellent room temperature stability of formulations of the type described in the present application is unexpected and surprising.

He further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made herein with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both pursuant to Title 18, Section 1001, United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

June 7, 1990

(Date)
This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined. This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 3 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I  THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
5. Information on How to Effect Drawing Changes, PTO-1474.
6. - are pending in the application.

Part II  SUMMARY OF ACTION

1. Claims _______________ are pending in the application.
   Of the above, claims _______________ are withdrawn from consideration.

2. Claims _______________ have been cancelled.

3. Claims _______________ are allowed.

4. Claims _______________ are rejected.

5. Claims _______________ are objected to.

6. Claims _______________ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _______________. Under 37 C.F.R. 1.84 these drawings are □ acceptable, □ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _______________, has (have) been □ approved by the examiner. □ disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed on _______________, has been □ approved. □ disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has □ been received □ not been received □ been filed in parent application, serial no. _______________; filed on _______________.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)
1 The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

2 Claims 21-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Klein et al in view of Stoughton, Smith and Merck Index for reasons of record. Applicants arguments are not deemed persuasive since a combination of known ingredients for their expected additive effects is the epitome of obviousness. The determination of an optimum pH range to employ is within the skill of the art. The Klein declaration was amply commented upon in the parent application.

3 Claims 21-24 are rejected on the ground of res judicata for reasons of record. The functional limitations of claim 21 are not deemed to change the material elements of the claim.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

LEGRAND SCHENKMAN
EXAMINER
ART UNIT 125

May 25, 1993
NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed 6/7/93.

2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.

3. ☐ Applicant's failure to timely file the response received ________________ within the period set in the Office letter.

4. ☐ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of ________________ of the Notice of Allowance.

☐ The issue fee was received on ________________.

☐ The issue fee has not been received in Allowed Files Branch as of ________________.

In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.318(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.

5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by ________________ as required in the last Office action.

☐ The corrected and/or substitute drawings were received on ________________.

6. ☐ The reason(s) below.

PTO-1432 (REV. 5-83)
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Robert W. Klein
Serial No.: 07/891,449
Group No.: 1205
Filed: May 29, 1992
Examiner: L. Schenkman

For: ANTI-ACNE METHOD AND COMPOSITION

Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTICE OF APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD
OF PATENT APPEALS AND INTERFERENCES

Applicant hereby appeals to the Board from the decision of the Primary Examiner mailed June 7, 1993 finally rejecting claims 21 - 24.

The item(s) checked below are appropriate:

1. STATUS OF APPLICANT
This application is on behalf of

X other than a small entity

small entity

Verified Statement

attached

already filed on

2. FEE FOR FILING NOTICE OF APPEAL
Pursuant to 37 CFR 1.17(e) the fee for filing the Notice of Appeal is:

X other than a small entity $270.00

Notice of Appeal fee due $270.00

Page 1 of 3
3. EXTENSION OF TERM

NOTE: The time periods set forth in 37 CFR 1.191 are subject to the provisions of §1.136 for patent applications 37 CFR 1.191(d). (But see 37 CFR 1.645 for extension of time in interference proceedings and 37 CFR 1.550(e) for extension of time in reexamination proceedings.)

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington D.C. 20231.

Deborah W. Bacon
(Type or print name of person mailing paper)

Date: December 7, 1993
(Signature of person mailing paper)

Certified True

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply.

(a) x Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)-(d)) for the total number of months check below:

<table>
<thead>
<tr>
<th>Extension (months)</th>
<th>Fee for other than small entity</th>
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</tr>
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<tbody>
<tr>
<td>one month</td>
<td>$110.00</td>
<td>$55.00</td>
</tr>
<tr>
<td>two months</td>
<td>$360.00</td>
<td>$180.00</td>
</tr>
<tr>
<td>three months</td>
<td>$840.00</td>
<td>$420.00</td>
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<td>four months</td>
<td>$1,320.00</td>
<td>$660.00</td>
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Fee $840.00

If an additional extension of time is required please consider this a petition therefor.

(check and complete the next item, if applicable)

___ An extension for ______ months has already been secured and the fee paid therefor of $_______ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $840.00

OR

(b) ___ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.
4. **TOTAL FEE DUE**

The total fee due is:

- Notice of Appeal fee $270.00
- Extension fee (if any) $840.00

**TOTAL FEE DUE** $1,110.00

5. **FEE PAYMENT**

- X Attached is a check in the sum of $1,110.00
- ___ Charge Account No. 19-5425 the sum of $

A duplicate of this transmittal is attached.

6. **FEE DEFICIENCY**

**NOTE:** If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, 1055 O.O. 31-33.

- X If any additional extension and/or fee is required, charge Account No. 19-5425.

**AND/OR**

- X If any additional fee for claims is required, charge Account No. 19-5425

Reg. No. 22,702

Tel. No. (215) 923-4466

Alexis Barron

Type or print name of attorney

Synnestvedt & Lechner

Name of Firm

1101 Market Street, Suite 2600

P. O. Address

Philadelphia, PA 19107
Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

The holding of Abandonment mailed January 5, 1994 has been withdrawn.

The application has been returned to pending status.

The error is regretted.

[Signature]

Docket Clerk, 1245
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants in the above-identified application hereby petition for a two-month extension of time, to and including April 10, 1994, for filing an Appeal Brief filed December 10, 1993.

Please charge the two-month extension fee of $360.00 and any additional fees, or credit any overpayment, to Deposit Account No. 18-1982. Two additional copies of this Petition are enclosed.

Respectfully submitted,

ROBERT W. KLEIN ET AL.

P 30343 04/20/94 07891449
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. A0430D US

Anticipated Classification of this application:
Class ______ Subclass ______

Serial Number: 07 / 891,449

PRIOR APPLICATION Examiner: L. Schenkman

Art Unit: 1205

Box FWC
Commissioner of Patents and Trademarks
Washington, D.C. 20231

FILE WRAPPER CONTINUING APPLICATION (FWC) TRANSMITTAL

WARNING: This form cannot be used where the parent case may not be abandoned since the filing of a request under the FWC procedure "will be considered to be a request to expressly abandon the prior application as of the filing date granted to the continuing application." 37 CFR 1.60.

WARNING: This procedure can only be used for a pending application prior to payment of the issue fee. 37 CFR 1.62(a) except if the parent application was withdrawn under 37 CFR 1.313(b)(5) "to permit consideration of an information disclosure statement under 1.97 in a continuing application." See Notice of January 9, 1992 (135 O.G. 13-25 at 21).

WARNING: The filing of an application at the United States stage of an international application requires an oath or declaration. 37 CFR 1.61(a)(4).

WARNING: The claims of this new application may be finally rejected in the first Office action where all claims of the new application are drawn to the same invention claimed in the earlier application and would have been properly finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. MPEP § 706.07(b).

WARNING: An application under 37 CFR 1.62 is filed by making changes by amendment to the prior application, 37 CFR 1.62(a), and not by filing a new application.

WARNING: Filing under 37 CFR 1.62 is permitted only if filed by the same or less than all the inventors named in the prior application. 37 CFR 1.61(a)(4).

This is a request for a filing under the file wrapper continuing application procedure, 37 CFR 1.62, for a

☑ continuation
☐ divisional
☐ continuation-in-part (for oath or declaration see III below)

attached is an amendment for added subject matter

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this FWC Transmittal and the documents referred to as attached therein are being deposited with the United States Postal Service on this date April 8, 1994 in an envelope as "Express Mail Post Office to Addressee" mailing Label Number GB761720157 US, addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(Type or print name of person mailing paper)

(Signature of person mailing paper)

NOTE: Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. (37 CFR 1.10(b)).

(FWC [4-2]—page 1 of 10)
continuing application to permit consideration of an information disclosure statement under 37 CFR 1.97.

NOTE: The filing date under 37 CFR 1.62(a) is "... the date on which a request is filed for an application... including identification of the Serial Number, filing date and applicant's name of the prior application." The prior application under 37 CFR 1.62(a) must be "... a prior complete application." According to 37 CFR 1.51(a) a prior complete application comprises: (1) a specification, including a claim or claims; (2) a declaration; (3) drawings; when necessary; and (4) the prescribed filing fee. Accordingly, as presently worded, 37 CFR 1.62(a) does not permit the FWC procedure to be used where the prior application is pending but only the processing and retention fee required by 37 CFR 1.21(1) is paid.

PARTICULARS OF PRIOR APPLICATION

A. Application Serial No. 07/891,449 filed May 29, 1992

B. Title (as originally filed and as last amended) ANTI-ACNE METHOD AND COMPOSITION

C. Name of applicant(s) (as originally filed and as last amended) and current correspondence address of applicant(s)
<table>
<thead>
<tr>
<th>3. FULL NAME OF INVENTOR</th>
<th>FAMILY NAME</th>
<th>FIRST GIVEN NAME</th>
<th>SECOND GIVEN NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>KLEIN</td>
<td>Robert</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **RESIDENCE & CITIZENSHIP**: Fort Washington, Pennsylvania, U.S.A.
- **POST OFFICE ADDRESS**: 510 Madison Ave., Pennsylvania 19034

<table>
<thead>
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<th>2. FULL NAME OF INVENTOR</th>
<th>FAMILY NAME</th>
<th>FIRST GIVEN NAME</th>
<th>SECOND GIVEN NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACKMAN</td>
<td>Albert</td>
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</table>

- **RESIDENCE & CITIZENSHIP**: Dresher, Pennsylvania, U.S.A.
- **POST OFFICE ADDRESS**: 3223 Lenape Dr., Pennsylvania 19025

- **RESIDENCE & CITIZENSHIP**: Dresher, Pennsylvania, U.S.A.
- **POST OFFICE ADDRESS**: 3223 Lenape Dr., Pennsylvania 19025

☑ Continued on added page for Inventor's Data
The above identified application, in which no payment of issue fee, abandonment of (other than where the above identified application was abandoned under 37 CFR 1.313(b)(5) to permit consideration of an information disclosure statement under 37 CFR 1.97), or termination of proceedings has occurred, is hereby expressly abandoned as of the filing date of this new application. Please use all the contents of the prior application file wrapper, including the drawings, as the basic papers for the new application.

It is understood that secrecy under 35 U.S.C 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 CFR 1.62 application, be it either this application or a prior application in the same file wrapper, the PTO may provide similar information or access to all the other applications in the same file wrapper.

II. Inventorship statement

NOTE: "If the continuation, continuation-in-part, or divisional application is filed by less than all the inventors named in the prior application a statement must accompany the application when filed requesting deletion of the names of the person or persons who are not inventors of the invention being claimed in the continuation, continuation-in-part, or divisional application." 37 CFR 1.62(a) [emphasis added].

NOTE: "In the case of a continuation-in-part application which adds and claims additional disclosure by amendment, an oath or declaration as required by § 1.63 must be filed. In those situations where a new oath or declaration is required due to additional subject matter being claimed, additional inventors may be named in the continuing application. In a continuation or divisional application which discloses and claims only subject matter disclosed in a prior application, no additional oath or declaration is required and the application must name as inventors the same or less than all the inventors in the prior application." 37 CFR 1.60(c).

(complete applicable item (a), (b) and/or (c) below)

(a) ☑ This application discloses and claims only subject matter disclosed in the prior application whose particulars are set out above and the inventor(s) in this application are

☒ the same

☐ less than those named in the prior application and it is requested that the following inventor(s) identified above for the prior application be deleted:

(type name(s) of inventor(s) to be deleted)

(FWC [4-2]—page 4 of 10)
(b) □ This application discloses and claims additional disclosure by amendment and a new declaration or oath is being filed. With respect to the prior application whose particulars are set out above the inventor(s) in this application are

□ the same
□ add the following additional inventor(s)

(type name of inventor(s) to be added)

(c) The inventorship for all the claims in this application is

□ the same
□ not the same, and an explanation, including the ownership of the various claims at the time the last claimed invention was made, is submitted.

III. Declaration or oath

A. Continuation or divisional

□ none required

B. Continuation-in-part

□ attached

executed by (check all applicable items)

□ inventor(s), 37 CFR 1.42 or 1.43.
□ legal representative of inventor(s), 37 CFR 1.42 or 1.43.
□ joint inventor or person showing a proprietary interest for inventor who refused to sign or cannot be reached, 37 CFR 1.47;
□ This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. (See item VIII below for fee.)

□ not attached

□ Application is made by a person authorized under 37 CFR 1.41(c) on behalf of all of the above named applicant(s). (The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently.)

□ Attached is a showing that the filing is authorized. (Not required unless called into question. 37 CFR 1.41(d).)

IV. Identification of Claims for Further Prosecution

WARNING: "The claims of a new application may be finally rejected in the first Office action in those situations where (1) the new application is a continuing application of, or a substitute for, an earlier application, and (2) all the claims of the new application (a) are drawn to the same invention claimed in the earlier application, and (b) would have been properly finally rejected on the grounds of art of record in the next Office action if they had been entered in the earlier application." MPEP, § 706.07(b).

□ The fees to be charged are to be based on the number of claims remaining as a result of the:

□ attached preliminary amendment.

□ the unentered amendment filed under 37 CFR 1.116 in the prior application, which is now repeated.

□ the claims as on file in the prior application.

V. Fee Calculation (37 CFR 1.16)

NOTE: The filing fee for a continuation, continuation-in-part, or divisional application is based on the number of claims remaining in the application after entry of any preliminary amendment and entry of any amendments under 37 CFR 1.116 unentered in the prior application which is requested to be entered in this FWC application. 37 CFR 1.62.
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- The fee for extra claims is not being paid at this time.

Filing fee calculation $710.00

**NOTE:** If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).

### VI. Petition for Suspension of Prosecution for the Time Necessary to File an Amendment

**NOTE:** Where it is possible that the claims on file will give rise to a first action final for this continuation application and for some reason an amendment cannot be filed promptly e.g., experimental data is being gathered) it may be desirable to file a petition for suspension of prosecution for the time necessary.

- There is provided herewith a Petition to Suspend Prosecution for the time Necessary to File an Amendment (New Application Filed Concurrently).

### VII. Small Entity Statement

- A verified statement that this is a filing by a small entity is attached.
- The small entity statement was filed in the parent application Serial No. 0 /______________ which parent application was filed on ___________ and this status is still proper and its benefit under 37 CFR 1.28(a) is hereby claimed.

Reduced filing fee calculation (50% of above) $_______

**NOTE:** 37 CFR 1.28(a) states "Status as a small entity must be specifically established by a verified statement filed in each application or patent in which the status is available and desired, except those applications filed under § 1.60 or § 1.62 of this part where the status as a small entity has been established in a parent application and is still proper."

The last sentence of 37 CFR 1.28(a) states: "Applications filed under § 1.60 or § 1.62 of this part must include a reference to a verified statement in a parent application if status as a small entity is still proper and desired."

Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee then the excess fee paid will be refunded on request. 37 CFR 1.28(a).

### VIII. Fee Payment Being Made at This Time

- Not attached
- No filing fee is submitted. (This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.)

Attached (FWC[4-2]—page 6 of 10)
filing fee $ 710.00

recording assignment ($40.00; 37 CFR 1.21(h)). For payment of fee see item XIV below.

petition fee for filing by other than all the inventors or person not the inventor where inventor refused to sign or cannot be reached ($130.00; 37 CFR 1.47 and 1.17(h)) $_____________

processing and retention fee ($130.00; 37 CFR 1.53(d) and 1.21(l)) $_____________

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78 indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be timely paid or the processing and retention fee in § 1.21(l) must be paid within 1 year from the notification under § 1.53(d).

Total fees enclosed $ 710.00

IX. Method of Payment of Fees

Attached is check in the amount of $__________

Charge Account No. 18-1982 in the amount of $ 710.00

A duplicate of this request is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

X. Authorization to Charge Additional Fees

WARNING: If no fee payment is made at this time this item should not be completed.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claim charges are authorized.

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to Account No. 18-1982:

37 CFR 1.16(a), (f) or (g) (filing fees)

37 CFR 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)) it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

37 CFR 1.17 (application processing fees)

WARNING: While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under § 1.136(a) this authorization should be made only with the knowledge that: "Submission of the appropriate extension fee under 37 CFR 1.136(a) is to no avail unless a request or petition for extension is filed" (Emphasis added). Notice of November 5, 1985 (7060 O.G. 27).

37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the Notice of Allowance, 37 CFR 1.311(b).

From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity. Notification of any change of status resulting in loss of entitlement to small entity status must be filed in the application prior to, or at the time of, paying the issue fee. 37 CFR 1.28(b).
XI. Instructions as to Overpayment

☐ Credit Account No. 18-1982

☐ Refund

XII. Priority—35 U.S.C. 119

☐ Priority of application Serial No. 0 / ________________ filed on ________________ in ________________ is claimed under 35 U.S.C. 119. (country)

☐ The certified copy has been filed on ________________ in prior U.S. application Serial No. 0 / ________________, which prior application was filed on ________________.

☐ certified copy will follow

XIII. Relate Back—35 U.S.C. 120

☐ Amend the specification by inserting before the first line the sentence:

"This is a ____________________________

☐ continuation

☐ divisional

☐ continuation-in-part

of copending application(s)

☐ Serial Number 07/891,449 filed on May 29, 1992 (cont.)

☐ International Application ________________ filed on ________________ and which designated the U.S.

(cont'd) which is a continuation of Serial No. 07/243,883, filed September 13, 1988, which is a continuation-in-part of Serial No. 661,951, filed July 27, 1987, which is a continuation of Serial No. 808,627, filed December 12, 1985.

NOTE: The proper reference to a prior filed PCT application which entered the U.S. national phase is the U.S. serial number and the filing date of the PCT application which designated the U.S.

XIV. Assignment

☐ The prior application is assigned of record to __________________________

☐ An assignment of the invention to __________________________ is attached. A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

NOTE: "If an assignment is submitted with a new application, send two separate letters - one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

XV. Power of Attorney

The power of attorney in the prior application is to

James A. Nicholson, Reg. No. 25,478; Alexis Barron, Reg. No. 22,702;

(Assigny) Martin F. Savitzky, Reg. No. 29,699 (Reg. No.)

 FW C [4-2]-page 8 of 10
a. □ The power appears in the original papers in the prior application.
b. □ The power does not appear in the original papers, but was filed on ______.
c. □ A new power has been executed and is attached.
d. ☑ Address all future communications to:
   Ross J. Oehler, Esq. 33,270
   Rhône-Poulenc Rorer Inc. (Reg. No.)
   500 Arcola Road, #3043 (Address) (610) 454-3883
   Collegeville, PA 19426 (Tel. No.)

   (Item d may only be completed by applicant, or attorney or agent of record.)

XVI. Maintenance of Copendency of Prior Application

(This item must be completed and the necessary papers filed in the prior application if the period set in the prior application has run)

☐ A petition, fee and response has been filed to extend the term in the pending prior application until April 10, 1994

NOTE: The PTO finds it useful if a copy of the petition filed in the prior application extending the term for response is filed with the papers constituting the filing of the continuation application. Notice of November 5, 1985 (1060 O.G. 27).

☐ A copy of the petition for extension of time in the prior application is attached.

XVII. Conditional Petitions for Extension of Time in Prior Application

(complete this item and file conditional petition in prior application if previous item not applicable)

☐ A conditional petition for extension of time is being filed in the pending prior application

NOTE: The PTO finds it useful if a copy of the petition filed in the prior application extending the term for response is filed with the papers constituting the filing of the continuation application. Notice of November 5, 1985 (1060 O.G. 27).

☐ A copy of the conditional petition for extension of time in the prior application is attached.

XVIII. Abandonment of Prior Application

☒ Please abandon the prior application at a time while the prior application is pending or when the petition for extension of time or to revive in that application is granted and when this application is granted a filing date so as to make this application copending with said prior application. At the same time please add the words "now abandoned" to the amendment to the specification set forth in XIII above.

NOTE: According to the Notice of May 13, 1983 (103 TMOQ 6-7), the filing of a continuation or continuation-in-part application is a proper response with respect to a petition for extension of time or a petition to revive and should include the express abandonment of the prior application conditioned upon the granting of the petition and the granting of a filing date to the continuing application.

NOTE: "A registered attorney or agent acting under the provisions of § 1.34(a), or of record, may also expressly abandon a prior application as of the filing date granted to a continuing application when filing such a continuing application." 37 CFR 1.138.

XIX. Information Disclosure Statement

☐ Submitted herewith is an Information Disclosure Statement
XX. Assignee Certification

WARNING: When an assignee files a continuation or divisional application (under 37 CFR 1.53, 1.60 or 1.62), reference may be made to a statement filed under 37 CFR 3.73(b) in the parent application or a copy of that statement may be filed. A newly executed statement under 37 CFR 3.73(b) must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-54.

(complete the following if the assignee is signing below)

☐ This is a ☐ continuation ☐ divisional application and the statement under 37 CFR 3.73(b)
☐ has been filed in the parent application.
☐ a copy of the previously filed statement in the parent application is attached.
☐ This is a continuation-in-part application and a "CERTIFICATE UNDER 37 CFR 3.73(b)" is attached.

(Type or print name of person signing declaration)

__________________________________________  ____________________________
Date                                      Signature

(P.O. Address of Signatory)

__________________________________________
(Tel. No. :(  ))

Reg. No.

__________________________________________

(if applicable)

☐ Inventor
☐ Assignee of complete interest
☐ Person authorized to sign on behalf of assignee
☐ Attorney or agent of record
☐ Filed under Rule 34(a)

(complete the following if applicable)

(type name of assignee)

(Address of assignee)

__________________________________________
(Title of person authorized to sign on behalf of assignee)

Assignment recorded in PTO on ______________

Reg. No. 29,699

☐ Plus ADDED PAGE FOR INVENTOR'S DATA FOR FWC FILING
☐ Plus ASSIGNMENT (DOCUMENT) COVER LETTER ACCOMPANYING
NEW PATENT APPLICATION

Signature of Attorney

__________________________________________

Reg. No.: (610) 454-3816

Martin F. Savitzky

(Type or print name of attorney)

Rhone-Poulenc Rorer Inc.

(P.O. Address)

500 Arcola Road; #3C43

Collegeville, PA 19426

FWC 4-2—page 10 of 10
An aqueous gel composition for the topical treatment of acne comprising a peroxide, an antibiotic of the lincomycin family and a surfactant.
The aqueous gel composition according to claim 25, wherein the peroxide comprises benzoyl peroxide, the antibiotic comprises clindamycin and the surfactant comprises dioctyl sodium sulfocuccinate.

The aqueous gel composition according to claim 25, comprising about 0.5 to about 3 weight percent of dioctyl sodium sulfocuccinate.

A method for treating acne comprising topical administration to a patient afflicted with acne of an effective amount of the composition according to claim 25.

A method for treating acne comprising topical administration to a patient afflicted with acne of an effective amount of the composition according to claim 26.

REMARKS

Claims 25-32 are presently in this application.

The Examiner will appreciate that the file wrapper in this case reflects a long history. It has always been Applicants' position that the novel composition recited in the claims demonstrates surprising and unexpected stability properties compared to previously existing topical acne treatments. Originally, during prosecution of the parent applications, it was believed that pH played a critical role in the surprising and unexpected stability characteristics exhibited by the claimed composition. Now, Applicants believe that pH, although related to optimal composition stability, is not the pivotal feature responsible for the non-obvious stability of the claimed composition. Applicants are currently conducting experiments to demonstrate the surprising stability characteristics of the claimed composition compared to the prior art compositions and expect to demonstrate the results of these experiments to the Examiner in the present FWC continuing application. Should the Examiner desire to discuss the nature of the current experimentation, the Examiner is invited to call Applicants' attorney at the telephone number indicated below.
Examination of claims 25-32 is respectfully requested.

Respectfully submitted,

ROBERT W. KLEIN ET AL.

[Signature]

Martin F. Savitzky
Registration No. 28,699
Rhône-Poulenc Rorer Inc.
500 Arcola Road; #3C43
Collegeville, PA 19426
(610) 454-3816
This application has been examined. This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 3 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I

THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
5. Information on How to Effect Drawing Changes, PTO-1474.

Part II

SUMMARY OF ACTION

1. Claims 10 to 32 are pending in the application. Of the above, claims are withdrawn from consideration.

2. Claims 1 to 24 have been cancelled.

3. Claims are allowed.

4. Claims 15 to 32 are rejected.

5. Claims are objected to.

6. Claims are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on . Under 37 C.F.R. 1.84 these drawings are not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on has (have) been approved by the examiner.

11. The proposed drawing correction, filed on , has been approved. disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. ; filed on .

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other
Serial No. 08/225,409
Art Unit 1205

Claims 21 to 24 are canceled and new claims 25 to 32 are added in the instant File Wrapper Continuation of SN 07/891449.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 25 to 32 are rejected under 35 U.S.C. 103 as being unpatentable over S. B. Tucker et al., British Journal of Dermatology. The reference teaches a combination for the topical treatment of acne comprising two antibiotics. Topical clindamycin phosphate and benzoyl peroxide are among the antibiotics discussed. Tucker suggests a combination the two active ingredients may be syneristic due to the differing mechanisms by which they appear to improve acne lesions. The claims differ in that the concentrations of each antibiotics, as well as additional ingredients potentially present in the topical composition, are not taught. However, one having ordinary skill
in the art would be motivated to produce a topical product for
the treatment of acne that is stable over a substantial period of
time and at certain temperature variations. Such modification
would be obvious because it would be within the purview of the
skilled artisan in formulation chemistry, through no more than
routine experimentation, to produce a stable topical composition
comprising a peroxide and an antibiotic of the lincomycin family
that would remain substantially stable at a temperature of 50°C
for a period of 30 days.

No claim is allowed.

Any inquiry concerning this communication or earlier
communications from the examiner should be directed to Examiner
Spivack whose telephone number is (703) 308-4703.

Any inquiry of a general nature or relating to the status of
this application should be directed to the Group receptionist
whose telephone number is (703) 308-1235.

Spivack:1b
September 19, 1994
TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART ANT"O "CARO CARBON

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OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)


EXAMINER: P. Spinack
DATE: 9/1/94

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)
EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

Ross Oehler (1)
Phyllis Spivack (2)

Date of Interview: 10/20/94

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☑ Yes ☐ No. If yes, brief description: Stability comparison studies between Benzamayen and the instant invention.

Agreement ☑ was reached with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: 25 to 32

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: All rejections set forth in previous actions relating to parent applications are withdrawn. Applicants will present formal data demonstrating stability of the composition of benzoyl peroxide and alindamycin described herein.

(A fuller description, if necessary and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the Interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the Interview.

☒ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Robert W. Klein and Albert M. Packman
Serial No.: 08/225,409 Group Art Unit: 1205
Filing Date: April 8, 1994 Examiner: P. Spivack
For: ANTI-ACNE METHOD AND COMPOSITION

CERTIFICATE OF MAILING (37 CFR 1.8a)
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: Dec. 28, 1994

PETITION FOR EXTENSION OF TIME

Applicants in the above-identified application hereby petition for a one-month extension of time, to and including January 21, 1995, for responding to the Office Action mailed September 21, 1994.

Please charge the one-month extension fee of $110.00 and any additional fees, or credit any overpayment, to Deposit Account No. 18-1982. Two additional copies of this Petition are enclosed.

Respectfully submitted,

ROBERT W. KLEIN ET AL.

Ross J. Oehler
Registration No. 33,270
Rhône-Poulenc Rorer Inc.
500 Arcola Road, P.O. Box 1200
Collegeville, PA 19426-0107
(610) 454-3883
AMENDMENT AND RESPONSE TO OFFICE ACTION

This is responsive to the Office Action mailed September 21, 1994 (Paper No. 16) in the above-identified U.S. patent application.

AMENDMENT

In the Claims:

Please add new claims 33 and 34 as follows:

3’-33. The composition according to claim 25 having a pH of about 4.6 to about 5.7.
3’-34. The composition according to claim 25 having a pH of about 4.6 to about 5.7.--

REMARKS

Claims 25-34 are presently in this application.
New claims 33 and 34 set forth dependent claims, which recite particular embodiments of the composition of the present invention. No new matter has been added nor has the subject matter been materially altered.

Applicants express their appreciation for the courtesy extended to their undersigned counsel during the personal interview conducted October 20, 1994. The remarks below reiterate the substance of that interview.

Applicants acknowledge that all rejections set forth in previous Office Actions relating to parent applications have been withdrawn by the Examiner.

OUTSTANDING OFFICE ACTION

Claims 25-32 have been rejected under 35 U.S.C. § 103 as being unpatentable over S.B. Tucker et al., "Comparison of Topical Clindamycin Phosphate, Benzoyl Peroxide, and a Combination of the Two for the Treatment of Acne Vulgaris," British Journal of Dermatology, 110(4) (April 1994), pages 487-492. The Examiner takes the position in the Office Action that the reference teaches a combination for the topical treatment of acne comprising two antibiotics: topical clindamycin phosphate and benzoyl peroxide, in particular. The Examiner argues that Tucker et al. suggest a combination of these two active ingredients may be synergistic and that one of ordinary skill in the art would have been motivated to produce a topical composition comprising a peroxide and an antibiotic of the lincomycin family.

Because Applicants believe that the Examiner has mischaracterized the prior art reference as it relates to the present invention, this rejection is respectfully traversed.

TRAVERSAL

Tucker et al. disclose seriatim application of topical clindamycin phosphate and benzoyl peroxide. Specifically, Tucker et al. disclose that "Patients were instructed to use the medication twice daily (clindamycin phosphate alone, benzoyl peroxide alone, or benzoyl peroxide in the morning and clindamycin phosphate in the evening)." Tucker et al. at page 488. Nowhere do Tucker et al. teach or suggest a single composition comprising both clindamycin phosphate and benzoyl peroxide. Indeed, Tucker et al. merely conclude that "The combination of therapy including clindamycin phosphate (1% solution) in the morning and benzoyl
peroxide (5% gel) at night consistently demonstrated the best overall efficacy when the acne severity index is applied." Tucker et al. at page 491.

The claims of the present application, on the other hand, are directed to a composition for treating acne "comprising a peroxide and antibiotic of the lincomycin family" (see, e.g., claim 25 (emphasis added)). Moreover, the claims of the present application recite a composition as set forth above where the composition is stable at a temperature of 50°C for a period of thirty (30) days. As pointed out in the Preliminary Amendment filed April 8, 1994, Applicants believe that the claimed invention exhibits surprising stability characteristics compared to the prior art compositions. For example, the topical acne preparation, Benzamycin® (Dermik Laboratories, Inc., employer of the present Applicants), is a combination of erythromycin and benzoyl peroxide, is supplied to pharmacists with separate containers for the erythromycin-containing component and the benzoyl peroxide-containing component. This requires that a pharmacist compound the ingredients before dispensing. This separate packaging is necessary because benzoyl peroxide, a known oxidizing agent, causes rapid degradation of the erythromycin component, especially if the compounded product is not refrigerated.

Thus, one of ordinary skill in the art, having knowledge of the Benzamycin® preparation and knowing that Tucker et al. disclose separate application of clindamycin and benzoyl peroxide, would find no teaching or incentive to arrive at the stable lincomycin antibiotic/peroxide composition recited in the present claims. Indeed, both Benzamycin® and Tucker et al. teach away from such a stable combination.

To further illustrate the surprising advantage of the present invention versus known prior art, there is submitted herewith a Declaration Under 37 C.F.R. § 1.132 of Albert M. Packman, D.Sc., one of the inventors of the present application. While the Declaration is believed to be self-explanatory, it is pointed out that the Declaration sets forth experimental evidence demonstrating the surprising stability of the composition of the present invention at room temperature versus the prior art composition, Benzamycin®.

Because Tucker et al. do not teach or suggest treatment of acne with a single composition comprising clindamycin and benzoyl peroxide, because Tucker et al. do teach that use of clindamycin and benzoyl peroxide to treat acne is exercised separately and at different times of the day, and because it is known that conventional antibiotic/peroxide anti-acne compositions, such as Benzamycin®, are
not stable without refrigeration, the claimed invention would not have been obvious to one of ordinary skill in the art.

For the reasons set forth above, Applicants submit that claims 25-34 define an invention, which is nowhere taught or suggested by the prior art, either alone or in combination. Reconsideration of claims 25-32, consideration of new claims 33 and 34 and early passage to issue of claims 25-34 are respectfully requested.

Respectfully submitted,

ROBERT W. KLEIN ET AL.

Ross J. Oehler
Registration No. 33,270
Rhône-Poulenc Rorer Inc.
500 Arcola Road; #3C43
Collegeville, PA 19426
(610) 454-3883
CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: Dec 28, 1994

DECLARATION OF ALBERT M. PACKMAN, D.Sc.
UNDER 37 C.F.R. § 1.132

Albert M. Packman hereby declares that:

1. He has the degree of Doctor of Science by Philadelphia College of Pharmacy and Science awarded in 1956.

2. He is employed presently by Dermik Laboratories, Inc. and holds the position of Vice President and Technical Director of Dermik Laboratories, Inc.

3. He is a named inventor on the present application.

4. Under his direction and supervision, an experiment was conducted whereby two sets of antibiotic/peroxide combinations were prepared. In a first preparation, 3% erythromycin was combined with 5% benzoyl peroxide in a vehicle comprising Purified Water USP, Carbomer 940 NF, Sodium Hydroxide NF, SD Alcohol, Fragrance and Dioctyl Sodium Sulfosuccinate (commercial Benzamycin® preparation available from Dermik Laboratories, Inc.). About 3% erythromycin is a well-established concentration for topical use of erythromycin. In a second preparation, 0.945% clindamycin was combined with 5% benzoyl
peroxide in a vehicle comprising Purified Water USP, Carbomer 934 NF, Sodium Hydroxide NF and Dioctyl Sodium Sulfosuccinate. About 1% clindamycin is a well-established concentration for topical use [see, e.g., Tucker et al., "Comparison of Topical Clindamycin Phosphate, Benzoyl Peroxide, and a Combination of the Two for the Treatment of Acne Vulgaris," *British Journal of Dermatology*, 110(4) (1984) at page 487].

5. The two sets of preparations described in Paragraph 4 above were stored at room temperature. Samples of each of the preparations were taken at one week intervals (starting at week 1 for the erythromycin preparation and starting at week 4 for the clindamycin preparation). The amount of antibiotic (erythromycin or clindamycin) was measured at each interval and expressed in terms of percent of initial amount.

6. Table 1 attached hereto sets forth the numeric results of the periodic testing described in Paragraph 5 above. Figure 1 attached hereto graphically illustrates the numerical values determined for percent of original amount of antibiotic (erythromycin or clindamycin) over time.

7. Table 1 and Figure 1 show that, at room temperature, the amount of erythromycin in a benzoyl peroxide combination decreases steadily and rapidly over time while the amount of clindamycin in a benzoyl peroxide combination shows almost no decrease even after a period over three times as long as the period illustrated for the erythromycin preparation.

Albert M. Packman further declares that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, pursuant to Title 18, Section 1001, U.S. Code and such willful false statements may jeopardize the validity of application and any patent issuing therefrom.

Date: Dec. 28, 1994

Albert M. Packman, D.Sc.

Enclosures
## TABLE 1

Stability of Active/Benzoyl Peroxide Preparations at Room Temperature Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>% Erythromycin</th>
<th>% of Original</th>
<th>% Clindamycin</th>
<th>% of Original</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>3.00</td>
<td>100.0</td>
<td>0.945</td>
<td>100.0</td>
</tr>
<tr>
<td>1 week</td>
<td>2.76</td>
<td>92.0</td>
<td></td>
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</tr>
<tr>
<td>2 weeks</td>
<td>2.10</td>
<td>70.0</td>
<td></td>
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<tr>
<td>3 weeks</td>
<td>1.74</td>
<td>58.0</td>
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</tr>
<tr>
<td>4 weeks</td>
<td>1.20</td>
<td>40.0</td>
<td>0.947</td>
<td>100.2</td>
</tr>
<tr>
<td>8 weeks</td>
<td>0.941</td>
<td>99.6</td>
<td>0.941</td>
<td>99.6</td>
</tr>
<tr>
<td>12 weeks</td>
<td>0.920</td>
<td>97.4</td>
<td>0.920</td>
<td>97.4</td>
</tr>
</tbody>
</table>

## FIGURE 1

Degradation Profile

- **Erythromycin**
- **Clindamycin**
UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF ALLOWABILITY

PART I.
1. This communication is responsive to Amendment filed December 30, 1994.
2. All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. The allowed claims are 25 to 34, now renumbered 1 to 10.
4. The drawings filed on are acceptable.
5. Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received.
6. Note the attached Examiner’s Amendment.
7. Note the attached Examiner Interview Summary Record, PTOL-413.
8. Note the attached Examiner’s Statement of Reasons for Allowance.
9. Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.
A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE “DATE MAILED” indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).
1. Note the attached EXAMINER’S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. . CORRECTION IS REQUIRED.
   b. The proposed drawing correction filed on has been approved by the examiner. CORRECTION IS REQUIRED.
   c. Approved drawing corrections are described by the examiner in the attached EXAMINER’S AMENDMENT. CORRECTION IS REQUIRED.
   d. Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:
- Examiner’s Amendment
- Examiner Interview Summary Record, PTOL-413
- Reasons for Allowance
- Notice of References Cited, PTO-892
- Information Disclosure Citation, PTO-1449
- Notice of Informal Application, PTO-152
- Notice of Patent Drawings, PTO-848
- Listing of Bonded Draftsmen
- Other

Spinack
7033084703
NOTICE OF ALLOWANCE AND ISSUE FEE DUE

I. Review the SMALL ENTITY Status shown above.
   If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
   A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
   B. If the Status is the same, pay the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee’s responsibility to ensure timely payment of maintenance fees when due.
NOTICE OF ALLOWANCE

AND ISSUE FEE DUE

The application identifies above has been examined and is allowed for issuance as a patent. Prosecution on the merits is closed.

The issue fee must be paid within three months from the mailing date of this notice or this application shall be regarded as abandoned. This statutory period cannot be extended.

How to respond to this notice:

I. Review the small entity status shown above.
   A. If the status is changed, pay twice the amount of the fee due shown above and notify the Patent and Trademark Office of the change in status, or
   B. If the status is the same, pay the fee due shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your issue fee. Even if the issue fee has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the issue fee to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

Important reminder: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.
1. The following is an Examiner's Statement of Reasons for Allowance: An Amendment, Paper No. 19, and the Packman Declaration under 37 C.F.R 1.132, Paper No. 20, both filed December 30, 1994, are acknowledged. Applicants' arguments in response to the rejection of the claims under 35 U.S.C. 103 as being unpatentable over Tucker et al., British Journal of Dermatology, of record, have been found persuasive. Tucker does not teach or suggest a single composition comprising both clindamycin phosphate and benzoyl peroxide. Specifically, the instant invention is directed to a composition that is stable at a temperature of 50°C for a period of thirty days. Accordingly, claims 25 to 34 are novel and unobvious over the prior art and are allowed in view of the contemporary knowledge of the art.

Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably accompany the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."
Serial Number: 08/225409
Art Unit: 1205

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Spivack whose telephone number is (703) 308 4703.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Phyllis G. Spivack
04 March 1995
NOTICE OF ALLOWANCE AND ISSUE FEE DUE

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.
   If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
   A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
   B. If the Status is the same, pay the FEE DUE shown above.
   If the SMALL ENTITY is shown as NO:
      A. Pay FEE DUE shown above, or
      B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.
NOTICE OF ALLOWANCE
AND ISSUE FEE DUE

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.
PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS
APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above. If the SMALL ENTITY is shown as YES, verify your
current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the
   FEE DUE shown above and notify the patent and
   Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown
   above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE.
   Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned.
   If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number.
    Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of
maintenance fees. It is patentee’s responsibility to ensure timely payment of maintenance
fees when due.

PTOL-85 (REV. 12/93) (0651-0033)
**PART B—ISSUE FEE TRANSMITTAL**

MAILING ADDRESS:
This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence, including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the addressee entered in Block 2. If you are not directed otherwise, by (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate “FEE ADDRESS” for maintenance fee notifications with the payment of issue fee or thereafter. See reverse for Certificate of Mailing.

<table>
<thead>
<tr>
<th>INVENTORS NAME</th>
<th>12M1/0307</th>
</tr>
</thead>
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<tr>
<td>ROSS J. Oehler</td>
<td>RHONE-POULENC Rorer INC.</td>
</tr>
<tr>
<td>500 ARCOLA Rd., #3043</td>
<td>COLLEGEVILLE, PA 19426</td>
</tr>
</tbody>
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| TITLE OF INVENTION | ANTI-ACNE METHOD AND COMPOSITION |

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**RESPONSE ADDRESS CHANGE (Complete only if there is a change)**

<table>
<thead>
<tr>
<th>First Name</th>
<th>Applicant</th>
<th>ROBERT W.</th>
</tr>
</thead>
</table>

**FOR ASSIGNMENT**

<table>
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<th>NAME OF ASSIGNEE</th>
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<th>120</th>
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</tr>
</tbody>
</table>

**DO NOT USE THIS SPACE**

**NOTE:** The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

<table>
<thead>
<tr>
<th>(Authorized Signature)</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4/28/XX</td>
</tr>
</tbody>
</table>

**TRANSMIT THIS FORM WITH POST-CERTIFICATE FOR MAILING FOR INVENTORY**

**PTOL-480 (REV.12-03)(0851-0003)**
The Commissioner of Patents
and Trademarks

Has received an application for a patent
for a new and useful invention. The title
and description of the invention are en-
closed. The requirements of law have
been complied with, and it has been de-
termined that a patent on the invention
shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having
title to this patent the right to exclude
others from making, using or selling the
invention throughout the United States
of America for the term of seventeen
years from the date of this patent, sub-
ject to the payment of maintenance fees
as provided by law.

Bruce Lehman

Commissioner of Patents and Trademarks

Marjorie V. Turner
Attest
CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: Nov. 29, 1995

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231
ATTN: Decision and Certificate of Corrections
Branch of the Patent Issue Division

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. 1.322

Sir:

It is respectfully requested that a Certificate of Correction be issued by the Patent and Trademark Office under 37 C.F.R. 1.322. A Certificate of Correction Form, in duplicate, is enclosed. There is no charge to correct the error which appears in the printed patent as it is a result of the Patent Office's mistake.

VM90188 01/29/96 5446028 18-1982 090 145 100.00CH
At column 1, line 31, please insert --used-- after the word "extensively".

At column 1, line 32, please insert --been-- after the word "not".

At column 4, line 1, please correct "941" to read --934--.

The Commissioner is hereby authorized to charge payment of the fee for ten (10) additional copies of the certified Certificate of Correction of U.S. Patent No. 5,446,028 to Deposit Account No. 18-1982. An original and two duplicates of this request are enclosed.

Respectfully submitted,

ROBERT W. KLEIN ET AL.

Ross J. Oehler
Registration No. 33,270
Rhône-Poulen Rorer Inc.
500 Arcola Road, P.O. Box 1200
Collegeville, PA 19426-0107
(610) 454-3883
At column 1, line 31, please insert --used-- after the word "extensively".

At column 1, line 32, please insert --been-- after the word "not".

At column 1, line 1, please correct "941" to read --934--.
NOTICE RE: CERTIFICATES OF CORRECTION

TO: CERTIFICATES OF CORRECTION BRANCH

The decision regarding the change(s) requested in the certificate of correction is shown below.

1. □ YES  □ NO  □ Comments below
2. □ YES  □ NO  □ Comments below
3. □ YES  □ NO  □ Comments below
4. □ YES  □ NO  □ Comments below
5. □ YES  □ NO  □ Comments below

□ Comments

SUPERVISORY PATENT EXAMINER
GROUP 120

Supervisor

Art Unit
NOTIFICATION REGARDING REQUEST FOR CERTIFICATE OF CORRECTION

The Certificate of Correction requested in the patent identified above has been APPROVED with the exception indicated below. The remaining errors will be corrected as requested. The Certificate, so modified, will be issued on MAY 2 8 1996.

A. THE CHANGES BELOW CANNOT BE INCLUDED IN THE CERTIFICATE SINCE THE REQUEST WAS FILED UNDER RULE 322:

1. Column __________, line __________, is printed in accordance with the record.
   (a) The change referred to was initialed and dated by applicant before execution of the application papers.

2. In column __________, line __________, the error resulted from applicant's failure to comply with Rule 121(a), in that the precise point of entry of the amendment was omitted.

3. In column __________, line __________, the alleged error is due to applicant's failure to comply with Rule 121(b), wherein provision is made for use of brackets, instead of parentheses, to cancel subject matter and for the use of interlineations to indicate new subject matter.

4. Omission of the priority data from the patent resulted from applicant's failure to fully comply with 35 U.S.C. 119, in that:
   (a) The priority data was omitted from the oath, or declaration
   (b) The claim for priority was not included in the application papers.
   (c) The certified copy of the foreign application was not filed.

5. Since, the inventor name(s) is/are printed in accordance with the type written signature, no correction is in order here, unless a petition is granted (See Petition filing information below).

6. The assignment data is printed in the patent in accordance with PTO-85b, submitted by applicant at time of payment of the base issue fee, no correction is in order here, unless a petition is granted (See Petition filing information below).

Any petition should be directed to the attention of the Assistant Commissioner for Patents, using the following mailing address or FAX number.

By Mail: Commissioner of Patents and Trademarks
Box DAC
Washington, D.C. 20231
OR
By FAX: (703) 308-6916
Attn: Office of Petitions

7. In column __________, line __________, the error arose because Rule 1.52(a) or 1.52(b) was not complied with. Consequently, words on top of certain pages were obliterated or not legible causing the Office to provide what appeared to be the proper words.

B. THE REQUEST HAS BEEN CHANGED AS SHOWN BELOW TO COMPLY WITH THE RECORD:

1. The error complained of in column __________, line __________, occurred in column __________, line __________, where the changes will be made.

2. The change requested in __________ has been modified by:
C. THE FOLLOWING CORRECTION CANNOT BE INCLUDED IN THE CERTIFICATE: THE REASONS GIVEN BELOW:

1. The word __________, purported to be in column __________, line __________, cannot be found in the printed patent.

2. The alleged error in column __________, line __________, is an editing change made in accordance with the style of the Invention Patent Manual.

3. In column __________, line __________, the alleged error is in fact a change made by the examiner and considered to be in accordance with the permissible amendments enumerated in M.P.E.P. 1302.04.

4. In the title, it is the practice to exclude words such as "Improvements in", "New", "A", "Novel", etc., from the printed patent.

5. Comparison of the patent in column __________, line __________, with the corresponding location in the application file reveals that there is no discrepancy.

6. The numbering of the claims and their dependency in the printed patent is in accordance with the renumbering of dependent claims by the examiner as described in M.P.E.P. 608.01(n).

7. The alleged error in column __________, line __________, is a change made in an Examiner's Amendment at time of allowance. Since no error is involved and since applicant filed no objection prior to payment of the base issue fee, the requested change will not be included in the Certificate.

8. The error complained of in column __________, line __________, cannot be corrected since:

D. ADDITIONAL CORRECTIONS:

Column 3, line 68, "941" should read --940--.

E. OTHER (Fee not enclosed):

FOR ADDITIONAL INFORMATION REGARDING THIS NOTIFICATION PLEASE CONTACT:

Michelle Williams
Certificates of Correction
(703) 305-8364

WITHIN 4 WEEKS FROM MAILING DATE OF THIS NOTIFICATION

This decision is rendered pursuant to authority delegated by the Solicitor under authority delegated to him by the Commissioner of Patents and Trademarks.

Form PTOL-464 (rev. 5/94)
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,446,028
DATED - : August 29, 1995
INVENTOR(S) : Robert W. Klein and Albert M. Packman

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 1, line 31, please insert --used-- after the word "extensively".

At column 1, line 32, please insert --been-- after the word "not".
At column 1, line 68, please correct "941" to read --940--.
At column 4, line 1, please correct "941" to read --934--.

Signed and Sealed this Twenty-eighth Day of May, 1996

BRUCE LEHMAN
Commissioner of Patents and Trademarks

Attest:

BRUCE LEHMAN
Attesting Officer
PATENT APPLICATION SERIAL NO. 07/891449

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

050 LP 06/10/92 07891449 1 101 690.00 CK 14,743-C-USA

PTO-1556
(5/87)
### PATENT APPLICATION FEE DETERMINATION RECORD

**Effective October 1, 1992**

#### CLAIMS AS FILED - PART I

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** troll 1**

** Docket Number: 08/225407

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**Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE**
**PATENT APPLICATION FEE DETERMINATION RECORD**

**Effective December 16, 1991**

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- **Docket Number:** 14143
- **Patent Number:** 06945
- **Foreign Patent Number:** 073458
- **Application Number:** 10
- **Claims:** 10
- **Independent Claims:** 1
- **Total Claims:** 10

### Drawings

- **Date:** 6-10
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**SEARCHED**

**SEARCH NOTES**

Check paper
SN 243, 283

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