Section 13.0
Patent Information

Patent No.	Expiration Date
4865883	August 11, 2004
5000886	March 19, 2008
5143661	March 19, 2008
5222529	June 29, 2010
5236355	August 17, 2010
5366733	March 19, 2008
5500228	March 19, 2008
5622498	August 17, 2010

The undersigned declares that the above listed Patents cover the delivery, process of manufacture, formulation composition and/or method of use, as well as the apparatus for filling and administration of minocycline PTS 1 mg. This product is the subject of this application for which approval is being sought.

2-3-00

J. R. Lawter, Ph.D.
Vice President
Product Development and Manufacturing

United States Patent [19]

Jernberg

[11] Patent Number: 4,685,883

[45] Date of Patent: Aug. 11, 1987

[54] **LOCAL DELIVERY OF CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PERIODONTAL DISEASE**

[76] Inventor: Gary R. Jernberg, 99 Navaho Ave. Ste. 102, Mankato, Minn. 56001

[21] Appl. No.: 759,513

[22] Filed: Jul. 26, 1985

Related U.S. Application Data

[63] Continuation of Ser. No. 530,999, Sep. 12, 1983, abandoned.

[51] Int. Cl.[4] A61C 5/00

[52] U.S. Cl. 433/215; 433/80; 433/136; 604/890

[58] Field of Search 433/215, 217, 135, 136, 433/80, 229; 604/890, 891, 892, 894, 896, 49, 54, 77; 128/136

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4,175,326	11/1979	Goodson	433/80
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(List continued on next page.)

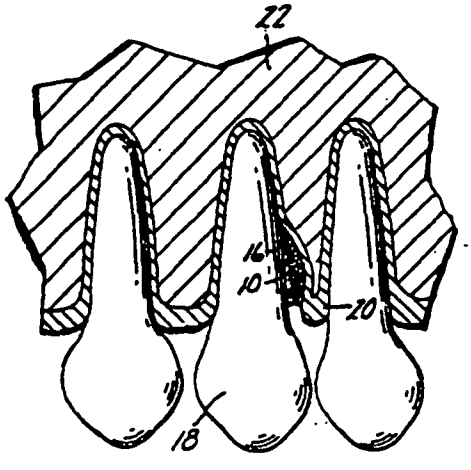
Primary Examiner—John J. Wilson

Attorney, Agent, or Firm—Merchant, Gould, Smith, Edell, Welter & Schmidt

[57] **ABSTRACT**

A method for local delivery of chemotherapeutic agent (12) to a localized site in the mouth is disclosed. The method of delivery includes displacement or reflection of gingival tissues (20) from the tooth, in the area to be treated, to facilitate access to the periodontal lesion (16). A biodegradable, time-release microsphere (10) capsulating the chemotherapeutic agent is next positioned in the lesion (16). Accordingly, localized delivery of chemotherapeutic agent (12) continuously over a predetermined period of time is provided.

7 Claims, 12 Drawing Figures



United States Patent [19]

Lawter et al.

[11] **Patent Number: 5,000,886**

[45] **Date of Patent: Mar. 19, 1991**

[54] **SILICONE-HARDENED PHARMACEUTICAL MICROCAPSULES AND PROCESS OF MAKING THE SAME**

[75] Inventors: **James R. Lawter, Goshen; Michael G. Lanzilotti, Pearl River, both of N.Y.**

[73] Assignee: **American Cyanamid COmpany, Stamford, Conn.**

[21] Appl. No.: **54,372**

[22] Filed: **May 26, 1987**

[51] **Int. Cl.**[5] **A61K 9/50**

[52] **U.S. Cl.** **264/4.3**; 264/4.6; 427/213.32; 427/213.36; 514/963; 424/460

[58] **Field of Search** 264/4.3, 4.6; 427/213.32, 213.36; 514/963; 424/460

[56] **References Cited**

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4,389,330	6/1983	Tice et al.	427/213.36
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4,732,763	3/1988	Beck et al.	514/932 X
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Primary Examiner—Robert L. Stoll
Assistant Examiner—Gary L. Geist
Attorney, Agent, or Firm—H. G. Jackson

[57] **ABSTRACT**

There is disclosed a process for preparing compositions comprising microcapsules by phase separation microencapsulation wherein the hardening agent employed is a volatile silicone fluid and with the compositions prepared thereby. The use of the volatile silicone fluid as a hardening agent permits the production of microcapsules substantially free of any alkane hardening agent, eliminating potential combustability problems of the prior art processes and toxicity problems of the prior art compositions.

36 Claims, No Drawings

US005143661A

United States Patent [19]

Lawter et al.

[11] Patent Number: 5,143,661

[45] Date of Patent: * Sep. 1, 1992

[54] SILICONE-HARDENED PHARMACEUTICAL MICROCAPSULES

[75] Inventors: James R. Lawter, Goshen; Michael G. Lanzilotti, Pearl River, both of N.Y.

[73] Assignee: American Cyanamid Company, Stamford, Conn.

[*] Notice: The portion of the term of this patent subsequent to Mar. 19, 2008 has been disclaimed.

[21] Appl. No.: 602,414

[22] Filed: Oct. 22, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 54,372, May 26, 1987, Pat. No. 5,000,886.

[51] Int. Cl.[5] A61K 9/50

[52] U.S. Cl. 264/4.3; 264/4.6; 427/213.32; 427/213.36; 514/963; 424/460

[58] Field of Search 264/4.3, 4.6; 427/213.32, 213.36; 514/963; 424/460

[56] References Cited

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4,935,171	6/1990	Bracken	264/4.6
4,954,381	9/1990	Cabasso et al.	264/4.6 X
5,000,886	3/1991	Lawter et al.	264/4.3

Primary Examiner—John S. Maples
Assistant Examiner—Gary L. Geist
Attorney, Agent, or Firm—James V. Costigan; H. G. Jackson

[57] ABSTRACT

There is disclosed a process for preparing compositions comprising microcapsules by phase separation microencapsulation wherein the hardening agent employed is a volatile silicone fluid and with the compositions prepared thereby. The use of the volatile silicone fluid as a hardening agent permits the production of microcapsules substantially free of any alkane hardening agent, eliminating potential combustability problems of the prior art processes and toxicity problems of the prior art compositions.

35 Claims, No Drawings

US005222529A

United States Patent [19]

Zoltan et al.

[11] Patent Number: 5,222,529

[45] Date of Patent: Jun. 29, 1993

[54] FILLING APPARATUS

[75] Inventors: Bart J. Zoltan, Old Tappan, N.J.; William F. Boulay, West Haverstraw, N.Y.; Donald R. Miller, Westwood, N.J.

[73] Assignee: American Cyanamid Company, Stamford, Conn.

[21] Appl. No.: 970,441

[22] Filed: Oct. 30, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 632,458, Dec. 21, 1990.

[51] Int. Cl.[5] B65B 31/00

[52] U.S. Cl. 141/4; 141/5; 141/67; 141/249; 137/888; 406/153; 406/146

[58] Field of Search 141/1, 4, 5, 67, 249, 141/46; 137/205.5, 564.5, 888; 417/86, 88; 222/630, 637; 406/146, 142, 153, 171; 128/203.15

[56] References Cited

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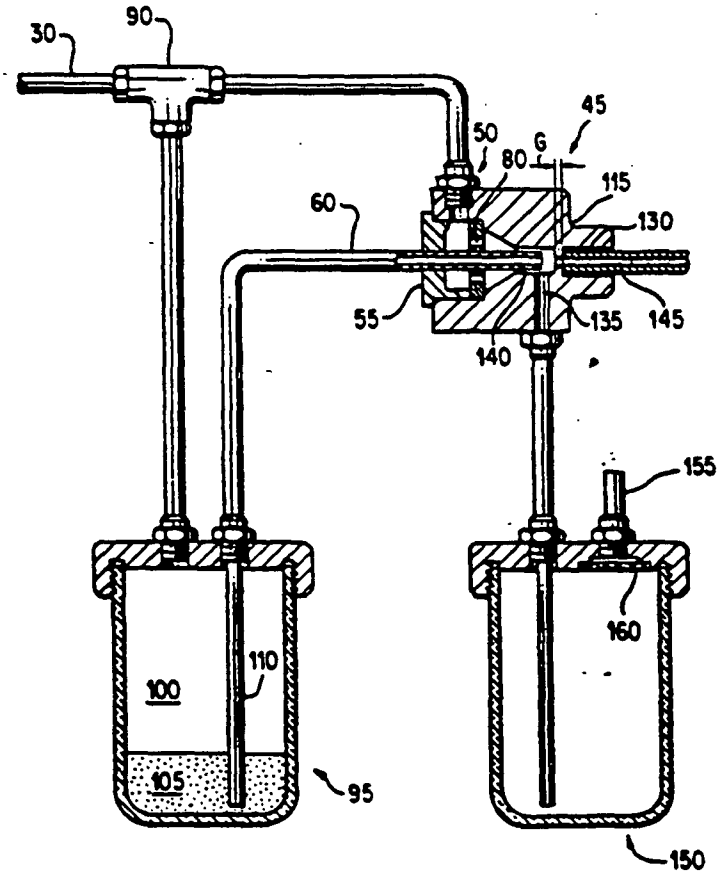
Primary Examiner—Henry J. Recla
Assistant Examiner—Steven O. Douglas
Attorney, Agent, or Firm—Thomas S. Szatkowski

[57] ABSTRACT

An apparatus for filling finely powdered material into a long and narrow cavity or hole having a relatively small opening is provided. The apparatus features a discharge port for a particulate laden gas stream directed toward the opening of the hole to be filled but spaced apart from the opening of the cavity to be filled by a gap, so that in operation the powdered material continues across the gap and into the cavity due to its inertia while the gas escapes through the gap.

18 Claims, 8 Drawing Sheets



US005236355A

United States Patent [19]

Brizzolara et al.

[11] Patent Number: 5,236,355

[45] Date of Patent: Aug. 17, 1993

[54] APPARATUS FOR THE TREATMENT OF PERIODONTAL DISEASE

[75] Inventors: Nancy S. Brizzolara, Congers; Michael G. Lanzilotti, Pearl River; James R. Lawter, Goshen, all of N.Y.

[73] Assignee: American Cyanamid Company, Stamford, Conn.

[21] Appl. No.: 593,125

[22] Filed: Oct. 5, 1990

Related U.S. Application Data

[62] Division of Ser. No. 289,076, Dec. 22, 1988, abandoned.

[51] Int. Cl.[5] A61G 17/02; A61C 5/04; A61M 5/00

[52] U.S. Cl. 433/80; 433/89; 604/187

[58] Field of Search 133/80, 89, 90; 604/181, 187, 189, 199

[56] References Cited

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4,685,883	8/1987	Jernberg	433/215
4,732,763	3/1988	Beck et al.	424/433
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4,780,320	10/1988	Baker	424/493
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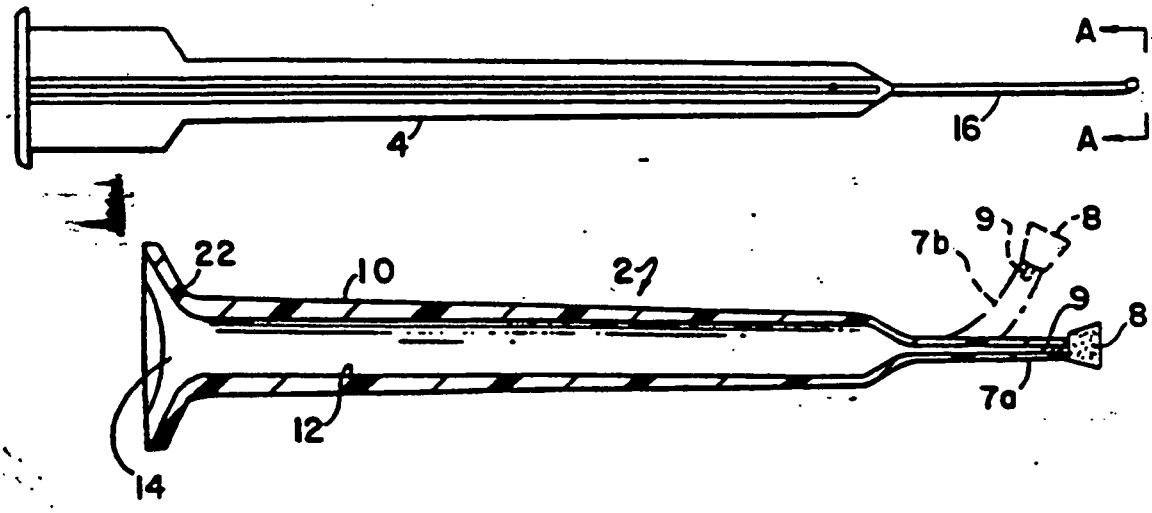
Primary Examiner—Robert P. Swiatek
Assistant Examiner—Cindy A. Cherichetti
Attorney, Agent, or Firm—H. G. Jackson; James V. Costigan

[57] ABSTRACT

Oral compositions for the local administration of a therapeutic agent to a periodontal pocket of a patient for alleviating dental disease comprise a plurality of dry, discrete microparticles each of which comprise an effective amount of at least one therapeutic agent dispersed in a matrix comprising a biocompatible and biodegradable polymer. Apparatus and methods are also provided for the dispensing of the dry microparticles to the periodontal pocket whereby they become tacky and adhere to the involved tissue so as to induce long term therapeutic benefits.

6 Claims, 6 Drawing Sheets



US005366733A

United States Patent [19]

Brizzolara et al.

[11] Patent Number: 5,366,733

[45] Date of Patent: * Nov. 22, 1994

[54] METHOD FOR THE TREATMENT OF PERIODONTAL DISEASE BY SUSTAINED DELIVERY OF A THERAPEUTIC AGENT TO THE PERIODONTAL POCKET, AND COMPOSITION OF MATTER THEREFOR

[75] Inventors: Nancy S. Brizzolara, Congers; Michael G. Lanzilotti, Pearl River; James R. Lawter, Goshen, all of N.Y.

[73] Assignee: American Cyanamid Company, Wayne, N.J.

[*] Notice: The portion of the term of this patent subsequent to Mar. 19, 2008 has been disclaimed.

[21] Appl. No.: 706,327

[22] Filed: May 28, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 289,076, Dec. 22, 1988, abandoned.

[51] Int. Cl.[5] A61K 6/00; A61K 9/52

[52] U.S. Cl. 424/426; 264/4.3; 264/4.6; 424/423; 424/435; 424/486; 424/489; 427/213.32; 427/213.36; 514/900; 514/963; 514/951

[58] Field of Search 424/486, 493, 426, 422, 424/423

[56] References Cited

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4,764,377	8/1988	Goodson	424/435
4,780,320	10/1988	Baker	424/493
4,917,893	4/1990	Okada et al.	424/423
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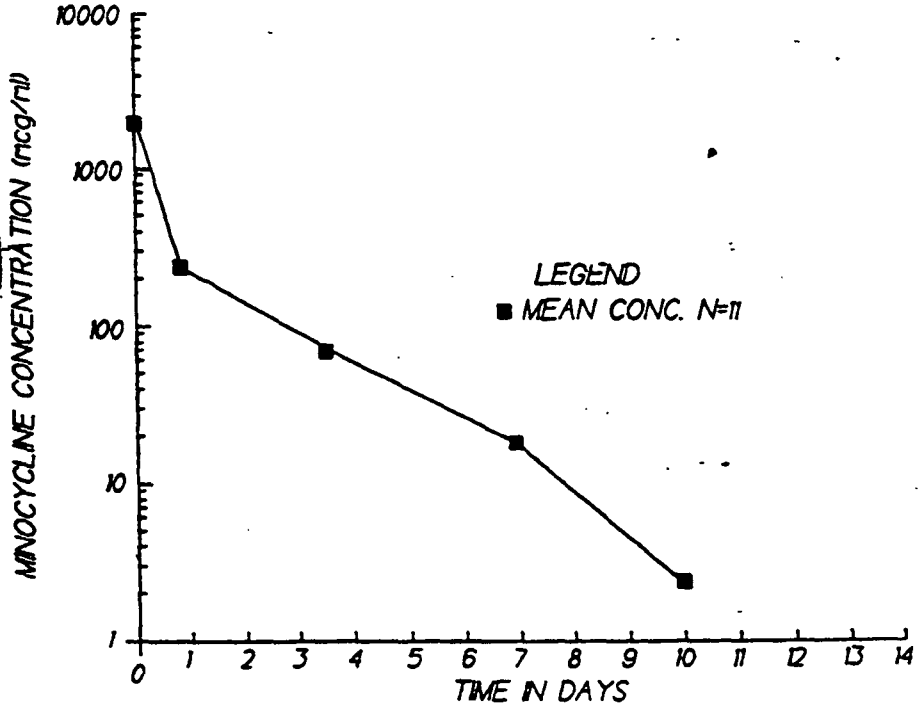
4,935,171	6/1990	Bracken	424/450
4,954,381	9/1990	Cabasso et al.	428/116
5,000,886	3/1991	Lawter et al.	264/4.3

Primary Examiner—G. S. Kishore
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—James V. Costigan; H. G. Jackson

[57] ABSTRACT

Oral compositions for the local administration of a therapeutic agent to a periodontal pocket of a patient for alleviating dental disease comprise a plurality of dry, discrete microparticles each of which comprise an effective amount of at least one therapeutic agent dispersed in a matrix comprising a biocompatible and biodegradable polymer. Apparatus and methods are also provided for the dispensing of the dry microparticles to the periodontal pocket whereby they become tacky and adhere to the involved tissue so as to induce long term therapeutic benefits.

35 Claims, 3 Drawing Sheets



US005500228A

United States Patent [19]

Lawter et al.

[11] Patent Number: 5,500,228

[45] Date of Patent: Mar. 19, 1996

[54] **PHASE SEPARATION-MICROENCAPSULATED PHARMACEUTICALS COMPOSITIONS USEFUL FOR ALLEVIATING DENTAL DISEASE**

[75] Inventors: **James R. Lawter, Goshen; Michael G. Lanzilotti, Pearl River, both of N.Y.**

[73] Assignee: **American Cyanamid Company, Madison, N.J.**

[*] Notice: The portion of the term of this patent subsequent to Mar. 19, 2008, has been disclaimed.

[21] Appl. No.: **617,382**

[22] Filed: **Nov. 26, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No. 288,739, Dec. 22, 1988, abandoned, which is a continuation-in-part of Ser. No. 54,372, May 26, 1987, Pat. No. 5,000,886.

[51] Int. Cl.[6] A61K 6/00; A61K 9/14; A61K 9/50; A61K 47/30

[52] U.S. Cl. 424/486; 424/426; 424/435; 514/900; 514/902

[58] Field of Search 424/78, 426, 435, 424/425, 460, 78.07, 486; 514/899, 900, 902

[56] **References Cited**

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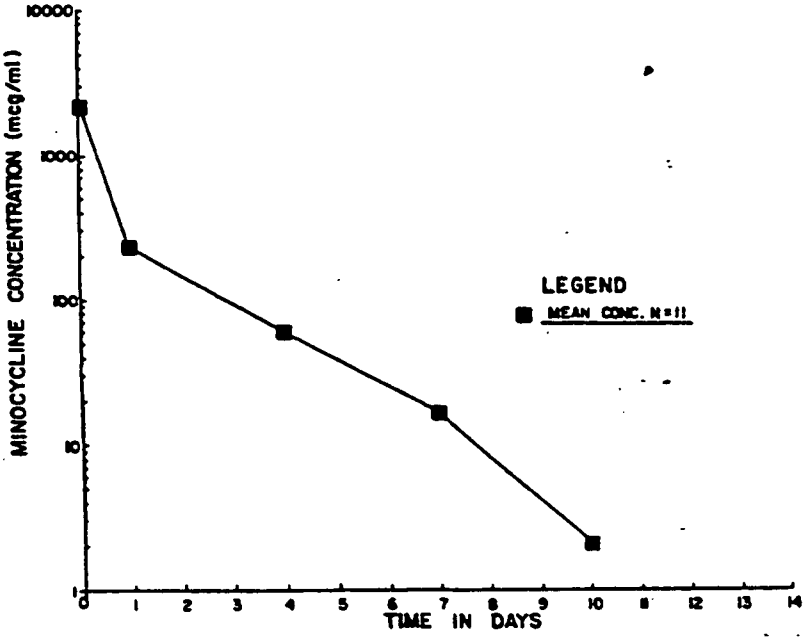
4,675,189	6/1987	Kent et al.	424/426
4,685,883	8/1987	Jernberg	604/890
4,764,377	8/1988	Goodson	424/449
4,780,320	10/1988	Baker	424/493

Primary Examiner—Jeffrey E. Russel
Attorney, Agent, or Firm—Hedman, Gibson & Costigan

[57] **ABSTRACT**

Oral compositions for the local administration of a therapeutic agent to a periodontal pocket of a patient for alleviating dental disease comprise a plurality of dry, discrete microparticles each of which comprise an effective amount of at least one therapeutic agent dispersed in a matrix comprising a biocompatible and biodegradable polymer of preferably, the dry microparticles and dispersed into the periodontal pocket whereby upon contact with the moist environment of the pocket, they hydrate, become tacky and adhere to one another and to the tissues surrounding the pocket so as to maintain intimate contact with the involved tissue so as to induce long term therapeutic benefits.

7 Claims, 6 Drawing Sheets



US005622498A

United States Patent [19]

Brizzolara et al.

[11] Patent Number: 5,622,498

[45] Date of Patent: * Apr. 22, 1997

[54] **METHOD FOR THE TREATMENT OF PERIODONTAL DISEASE BY SUSTAINED DELIVERY OF A THERAPEUTIC AGENT TO THE PERIODONTAL POCKET, COMPOSITION OF MATTER THEREFOR AND APPARATUS FOR THE ADMINISTRATION THEREOF**

[75] Inventors: **Nancy S. Brizzolara**, Congers; **Michael G. Lanzilotti**, Pearl River; **James R. Lawter**, Goshen, all of N.Y.

[73] Assignee: **American Cyanamid Company**, Madison, N.J.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,236,355.

[21] Appl. No.: 7,753

[22] Filed: Jan. 22, 1993

Related U.S. Application Data

[60] Continuation of Ser. No. 593,125, Oct. 5, 1990, Pat. No. 5,236,355, which is a division of Ser. No. 289,076, Dec. 22, 1988, abandoned.

[51] Int. Cl.[6] A61C 17/02; A61C 5/04; A61M 5/00

[52] U.S. Cl. 433/80; 433/89; 604/187

[58] Field of Search 433/80, 89, 90; 604/181, 187, 189, 199

[56] **References Cited**

U.S. PATENT DOCUMENTS

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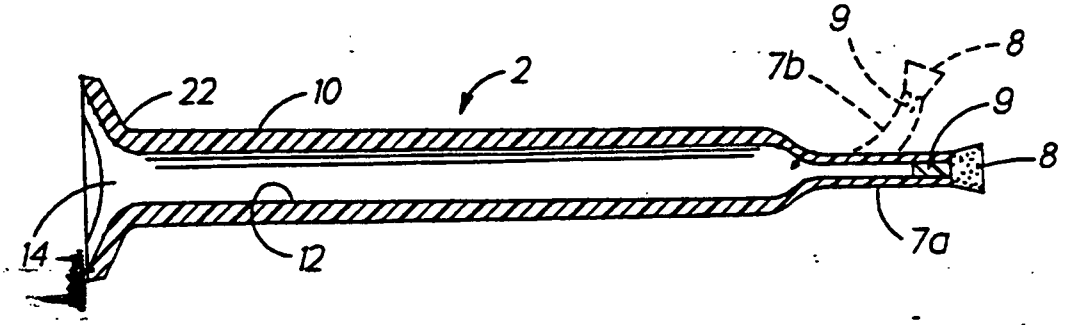
3,939,834	2/1976	McMahon	128/272
4,276,880	7/1981	Malmin	128/221
4,622,244	11/1986	Lapka et al.	427/213.32
4,685,883	8/1987	Jernberg	433/215
4,764,377	8/1988	Goodson	424/435
4,798,596	1/1989	Mühlbauer	604/218
4,863,072	9/1989	Perler	222/390
5,236,355	8/1993	Brizzolara et al.	433/80

Primary Examiner—Cary E. O'Connor
Attorney, Agent, or Firm—Hedman, Gibson & Costigan, P.C.

[57] **ABSTRACT**

Oral compositions for the local administration of a therapeutic agent to a periodontal pocket of a patient for alleviating dental disease comprise a plurality of dry, discrete microparticles each of which comprise an effective amount of at least one therapeutic agent dispersed in a matrix comprising a biocompatible and biodegradable polymer. Apparatus and methods are also provided for the dispensing of the dry microparticles to the periodontal pocket whereby they become tacky and adhere to the involved tissue so as to induce long term therapeutic benefits.

31 Claims, 4 Drawing Sheets



Section 14.0
Patent Certification

The undersigned certifies that the patents described in Section 13.0 were licensed to OraPharma, Inc.

J. R. Lawter 2-3-00

J. R. Lawter, Ph.D.
Vice President
Product Development and Manufacturing

Exclusivity Summary from FDA

EXCLUSIVITY SUMMARY for NDA # 50-781 SUPPL # __

Trade Name: **ARESTIN**
Generic Name: **(minocycline hydrochloride) microspheres 1mg**
Applicant Name: **ORAPHARMA** **HFD- 540**
Approval Date: **February 17, 2001**

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO/___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type (SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /_X__/ NO /__/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
      3 years

In letter from Applicant dated 1/9/01, market exclusivity is sought until Aug 17, 2010.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /__ _/ NO /_X_/

If yes, ~~NDA #~~ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	**50,315**	**Minocin Capsules**
NDA #	**50,427**	**Minocin**
NDA #	**50,444**	**Minocin Injection**
NDA #	**50,445**	**Minocin Oral Suspension**
NDA #	**50,451**	**Minocin**
NDA #	**50,649**	**Minocin Pellet-F3**

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X__/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/ N/A

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # **OPI-103A**

Investigation #2, Study # **OPI- 103B**

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new"to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # __

NDA # _____ Study # __

NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # **OPI-103 A**

Investigation #_, Study # **OPI-103B**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1: **OPI-103 A**

IND # _____ YES /_X__/ NO /___/ Explain

Investigation #2: **OPI-103 B**

IND # _____ YES /__X_/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X_/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer/Kalyani Bhatt/RPM

2-8-01

Date

/S/

Jonathan Wilkin, M.D./Division Director

2.15.01

Date

cc:

Sponsor's Request for Exclusivity

1-11-01

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974
215 956-2200 Tel
215 443-9531 Fax

January 11, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Market Exclusivity

Dear Dr. Wilkin:

Reference is made to 21CFR 314.108 (4) regarding market exclusivity for a new product having an active moiety that has been previously approved in another application under section 505(b) of the act.

OraPharma, Inc. has conducted clinical studies with the Arestin™ product containing minocycline, the active moiety, for the above referenced new drug application. OraPharma, Inc. therefore requests three (3) years market exclusivity.

Reference is also made to a telefax submitted to FDA on January 9, 2001 and NDA amendment No. 20.1 dated January 9, 2001, which was submitted erroneously due to a misunderstanding of a request made by the Division.

I hope this clarifies and satisfies your inquiry for OraPharma, Inc.'s market exclusivity request for the above reference product.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

[redacted] Sponsor Request for Exclusivity
[redacted]-09-01

OraPharma, Inc.
732 Louis Drive
Warminster, PA 18974
215-956-2200
Facsimile: 215-443-9531

ORAPHARMA INC.

FAX COVER SHEET

To:	Ms. Kalyani Bhatt, Project Manager	**From:**	Markus Herzig
Company:	FDA	**Date:**	January 9, 2001
Fax No.:	301-827-2091	**No. of pages w/cover:**	5
RE:	NDA-50-781		

[X] *Urgent* [ ] *Reply ASAP* [ ] *Please comment* [ ] *Please review* [ ] *For your information*

Dear Ms. Bhatt:

Attached is the **Marketing Exclusivity amendment to NDA 50-781.** If you have any questions, please don't hesitate to contact me.

Sincerely,

Markus Herzig

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974
215/956-2200 Tel
215/443-9531 Fax

January 9, 2001

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Arestin (minocycline hcl) microspheres, 1mg
Amendment: Marketing Exclusivity

Dear Dr. Wilkin:

Reference is made to a telephone call on January 9, 2001 by Ms. K. Bhatt in your Division with the undersigned in which she requested OraPharma, Inc. to officially request marketing exclusivity for the above referenced product according to the patents covering this product.

OraPharma, Inc. herewith requests market exclusivity until August 17, 2010 for Arestin™. August 17, 2010 is the date when the latest two patents (patent no. 5236355 and patent no. 5622498) expire.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

I also attached a copy of the cover letter dated June 5, 2000 (amendment 3.1) in which OraPharma, Inc. provided microbiology feedback to questions raised by Dr. Riley, for which we would appreciate receiving feedback as we have worked on finding a more sensitive method to measure bioburden.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs and Quality Assurance

Form FDA 356h
Submitted in duplicate

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

APPLICANT INFORMATION

NAME OF APPLICANT OraPharma, Inc.	DATE OF SUBMISSION January 9, 2001
TELEPHONE NO. *(Include Area Code)* 215-956-2200	FACSIMILE (FAX) Number (Include Area Code) 215-443-9531
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 732 Louis Drive Warminster, PA 18974	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Markus F. Herzig 732 Louis Drive Warminster, PA 18974

PRODUCT DESCRIPTION—

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 50-781

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Minocycline PTS (Minocycline Periodontal Therapeutic System)	PROPRIETARY NAME (trade name) IF ANY ARESTIN™
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 7 - dimethylamine - 6 - demethyl - 6 - deoxytetracycline hydrochloride	CODE NAME (If any) –

DOSAGE FORM: topical	STRENGTHS: 1 mg	ROUTE OF ADMINISTRATION: Subgingival

(PROPOSED) INDICATION(S) FOR USE: Adjunctive therapy to scaling and root planing procedures in patients with adult periodontitis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Requested Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NA

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NA

FORM FDA 356h (7/97)

This application contains the following items: *(Check all that apply)*

☐	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
☐	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
☐	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306 (k) (1))	
☐	17. Field copy certification (21 CFR 314.50(k) (3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Markus F. Herzig	Markus F. Herzig, Executive Director Regulatory Affairs and Quality Assurance	January 9, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

Please DO NOT RETURN this form to this address.

ITEM 16: DEBARMENT CERTIFICATION

Pursuant to Section 306 (k) (1) of the Food, Drug and Cosmetic Act, the undersigned certifies that OraPharma, Inc. did not and will not use in any capacity services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with the New Drug Application for TRADEMARK™ (minocycline PTS), NDA No. ——

Markus F. Herzig
Executive Director, Regulatory Affairs
OraPharma, Inc.

December 13, 1999

Markus F. Herzig
Executive Director, Regulatory Affairs
OraPharma, Inc.
732 Louis Drive
Warminster, Pennsylvania 18974

Dear Markus:

Applied Analytical Industries, Inc. (AAI) is a supplier of services to the pharmaceutical industry in general as well as to OraPharma, Inc. in particular. AAI carries out its operations in compliance with the current policies, guidelines and regulations promulgated by the Food and Drug Administration (FDA) under requirements of the Federal Food, Drug, and Cosmetic Act and related Acts.

Inasmuch as AAI provides pharmaceutical services to OraPharma, Inc. and the results of those services (records and data) may be used by OraPharma, Inc. in applications to the FDA seeking marketing approval, AAI now wishes to fulfill its obligation to OraPharma, Inc. by attesting to compliance with the Generic Drug Enforcement Act of 1992. Specifically:

1. Applied Analytical Industries, Inc. certifies that, in the course of supplying pharmaceutical services to OraPharma, Inc. in support of any of its drug marketing applications, it did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) of section 306 of the Generic Drug Enforcement Act of 1992.

2. Applied Analytical Industries, Inc. certifies that, to the best of its knowledge, no person in the firm or affiliated with the firm and responsible for the development or submission of records or data in support of any abbreviated drug application for OraPharma, Inc. has been convicted within the last five years of any crime described in subsections (a) and (b) of section 306 of the Generic Drug Enforcement Act of 1992.

Applied Analytical Industries, Inc. stands ready to provide OraPharma, Inc. with any additional information that may be required in support of the above certifications.

Sincerely,

Mark P. Hayes, Ph.D.
Regulatory Affairs
:nacks
cc: Marty Beasley (AAI)