CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Correspondence

Arent Fox
ATTORNEYS AT LAW

Wayne H. Matelski

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW Washington, DC 20036-5339
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COPY

BY COURIER

December 8, 1998

Document Room 9B-23
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
RESPONSE TO RECOMMENDATION OF LABELING AND NOMENCLATURE COMMITTEE

Dear Madam/Sir:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am responding to Dr. Cynthia McCormick's letter dated November 24, 1998 (see attached) concerning NDA 20-971. In her letter, Dr. McCormick noted that the FDA's Labeling and Nomenclature Committee recommended that the Sponsor change the proposed name for Septanest® — (articaine hydrochloride 4% with epinephrine 1/100,000) by replacing the "—" with the epinephrine dosage strength. The Sponsor has considered this recommendation and proposes the following new names for its two products:

Product	Name Proposed in NDA 20-971 Submitted on March 30, 1998	New Name Proposed
Articaine hydrochloride 4% with Epinephrine 1/100,000	Septanest® —	—
—	—	—

If you have any questions or comments concerning the proposed names, please contact me.

Thank you for your assistance.

Very truly yours,

Wayne H. Matelski/BW

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER
20-971

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Deproco, Inc.	December 8, 1998
TELEPHONE NO. *(Include Area Code)* 1-800-872-8305	**FACSIMILE (FAX) Number** *(Include Area Code)* 302-328-5653
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 245-C Quigley Blvd. New Castle, DE 19720	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone, & FAX number)* IF APPLICABLE Wayne Matelski, Esq. Arent Fox Kintner Plotkin & Kahn 1050 Connecticut Avenue, N.W. Washington, DC 20036-5339 Ph: 202-857-6340 F: 202-857-6395

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-971

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Reference Attachment	Septanest® and Septanest®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	**CODE NAME** *(If any)* N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
...lution for injection	Reference Attachment	Nerve block of infiltration

(PROPOSED) INDICATION(S) FOR USE:
For infiltration or nerve block anesthesia for dentistry

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 N/A 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 Response to Recommendation of Labeling and Nomenclature Committee

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

NUMBER OF VOLUMES SUBMITTED 1 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.

Reference Attachment

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

Reference Attachment

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)
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	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)
X	19. OTHER (Specify) Response to Recommendation of Labeling and Nomenclature Committee

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
Wayne H. Matelski/BW	Wayne Matelski, Esq. U.S. Agent	12/8/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1050 Connecticut Avenue, N.W. Washington, DC 20036-5339	(202) 857-6340

Attachment to FDA 356h
NDA 20-971

Established Name(s)

Septanest ®
Septanest ®

Articaine Hydrochloride 4% with Epinephrine 1:200,000
Articaine Hydrochloride 4% with Epinephrine 1:100,000

Strengths
Articaine Hydrochloride 4% with Epinephrine 1:100,000 or 1:200,000

Cross-References

Drug Master Files (DMFs)

DMF [redacted]
DMF
DMF [redacted]
DMF [redacted]
DMF
DMF [redacted]
DMF

Establishment Information

The drug product is manufactured by:

Spécialités Septodont
58, rue du Pont de Créteil
Saint-Maur-Des-Fossés
94100 Paris
France

The manufacturer of [redacted]

The manufacturer of [redacted]

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD 170/Nolan

Food and Drug Administration
Rockville MD 20857

NOV 24 1998

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialities Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ~~Septanest~~ (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We would like to share with you the recommendations of the Labeling and Nomenclature Committee regarding your proposed proprietary name.

In your submission you proposed ~~Septanest~~ as the tradename for your product. The Labeling and Nomenclature Committee recommends that you use the epinephrine dosage strength instead of using '~~—~~' and highlight the concentration to denote difference in strengths. The use of '~~—~~' following the name is misleading as in the United States "SP" means "Spinal." The proposed tradename Septanest was determined to be acceptable.

If you have any questions, contact Ken Nolan, Project Manager, at 301-827-7410.

Sincerely,

/S/

MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III

Arent Fox
ATTORNEYS AT LAW

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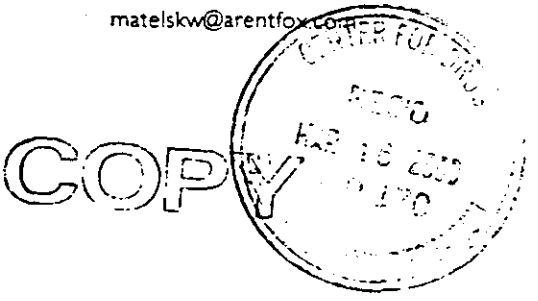
Wayne H. Matelski

Direct 202/857-6340
matelskw@arentfox.com



BY COURIER

March 16, 2000

Document Room 9B-23
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
RESPONSE TO FDA QUESTIONS

Dear Madam/Sir:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am responding to the questions/issues raised by the Agency during a teleconference on March 8, 2000. Set forth below are each of the questions/issues raised by the Agency followed by the Sponsor's response. As noted below, for some of the responses, the Sponsor is in the process of collecting additional information and will submit complete responses within the next week.

FDA QUESTION/ISSUE NO. 1

The FDA explained that the Agency's new nomenclature review committee raised a concern that dentists might confuse the names "Septanest®" and "Citanest®" -- a prilocaine dental anesthetic manufactured by Astra Pharmaceuticals, L.P., Westborough, Massachusetts as Citanest® Plain (without epinephrine) and Citanest® Forte (with 1:200,000 epinephrine) -- because, according to the committee, the names sound alike. The Agency explained that if a dentist confused the products and inadvertently administered the wrong product, this might lead to an adverse reaction in a patient sensitive to an ingredient that may be present in one product but not the other. The Agency requested that the Sponsor justify its choice of the name "Septanest®" and provide any information supporting the conclusion that the name would not be confused with "Citanest®."

SPONSOR'S RESPONSE

The Sponsor intends to submit a complete response to this issue within the next week.

FDA QUESTION/ISSUE NO. 2

The FDA asked the Sponsor to summarize the basis upon which the Sponsor determined that the imprinting on the cartridges would not rub off.

SPONSOR'S RESPONSE

The Sponsor has contacted the cartridge manufacturer, [redacted], and asked for the basis upon which that company has determined that the imprinting will not rub off the cartridges used for the Septanest® products. The Sponsor expects to receive a response to its request within the next few days and will submit this information to the FDA upon receipt. In the meantime, however, in order to facilitate the Agency's review, we have attached sample cartridges of other products that have been imprinted using the same process as will be used for the Septanest® cartridges (see Attachment A, which includes samples of (i) Septanest® 1:100,000 marketed in the United Kingdom, (ii) Septanest® 1:200,000 marketed in the United Kingdom, (iii) Scandonest® 3% Plain marketed in the U.S., and (iv) Lignospan® Standard marketed in the U.S.). As you will see from a physical inspection of these cartridges, the imprinting cannot be rubbed off. [Please note that the sample cartridges in Attachment A for the Septanest® products sold in the United Kingdom have a different cartridge volume and different label declarations from those to be marketed in the United States, as summarized in Amendment No. 3 to NDA 20-971, submitted on February 3, 2000.]

FDA QUESTION/ISSUE NO. 3

The Agency explained that its reviewers had tentatively concluded that NDA 20-971 would be classified as a 505(b)(2) application under which the Sponsor would receive 3 years market exclusivity as provided by Drug Price Competition and Patent Term Restoration Act. The Agency asked whether the Sponsor agreed with this classification and, if so, to modify its Form FDA 356h to reflect the 505(b)(2) classification.

SPONSOR'S RESPONSE

The Sponsor accepts the Agency's tentative conclusion to classify the NDA as a 505(b)(2) application with three years market exclusivity. The Sponsor has modified the Form FDA 356h attached to this letter to reflect this classification.

FDA QUESTION/ISSUE NO. 4

Because the Sponsor's products contain sodium metabisulfite, the Agency asked the Sponsor to ensure that its labeling contained appropriate sulfite warnings.

SPONSOR'S RESPONSE

The Sponsor intends to include the following sulfite warnings on its labeling:

Cartridge	"Contains sodium metabisulfite" (The draft cartridge labels submitted to the Agency with Amendment No. 3 to NDA 20-971 include this statement.)
Can and Box	"Contains sodium metabisulfite. See Warnings section of insert for details." (This text does not appear on the draft can and box labels submitted with Amendment No. 3 to NDA 20-971, but will be added to the final printed labeling.)
Package Insert	"Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people." (The draft insert submitted with Amendment No. 3 to NDA 20-971 already contains this warning as required by 21 C.F.R. § 201.22(b).)

In a conversation between my colleague Brian Waldman and Ms. Laura Governale on March 10, 2000, Ms. Governale explained that she felt that the warnings described above would be acceptable to the Agency.

FDA QUESTION/ISSUE NO. 5

The FDA asked the Sponsor to submit color mock-ups for the cartridge, can, and box labels.

SPONSOR'S RESPONSE

The Sponsor is in the process of preparing the color copies of the can and box labels. These labels will be sent from France on March 17, and I will submit them to the Agency upon receipt. Because of the substantial cost associated with imprinting the cartridges, the Sponsor would prefer not to submit sample cartridges for Septanest® until the FDA approves the label text, including the product name, for the cartridges. The Sponsor submitted the proposed text for the cartridges in Amendment No. 3 to NDA 20-971. Further, the Sponsor is sending to me samples of Septanest® cartridges [redacted] that use the same colors (blue [redacted] as are proposed for the U.S. products. I will submit these cartridges to the FDA upon receipt. We are hopeful that this information, when considered together, will enable the FDA to approve the cartridge labels.

FDA QUESTION/ISSUE NO. 6

On March 9, 2000, Ms. Governale contacted Mr. Waldman and asked that the Sponsor submit: (1) sample cartridges of the Septanest® products; and (2) copies of all labeling and packaging materials for samples, if the Sponsor intends to distribute samples to dentists.

SPONSOR'S RESPONSE

As noted in the Sponsor's Response to FDA Question/Issue No. 5 above, the Sponsor has not yet ordered imprinted cartridges for Septanest® because the text for the imprinting has not yet been approved by the Agency. However, the Sponsor has submitted the proposed text for the cartridge as well as sample cartridges of similar dental anesthetics produced using the same imprinting process as will be used to produce the Septanest® cartridges. The Sponsor is hopeful that the Agency will be able to determine the acceptability of the proposed Septanest® cartridges after analyzing the proposed text and the attached samples.

Finally, the Sponsor does not at this time intend to distribute drug samples to dentists.

* * * * *

The Sponsor will submit complete responses to the FDA Question/Issue Nos. 1, 2, and 5 within the next week. The Sponsor respectfully requests that the Agency complete its review by April 3, 2000, the primary user fee goal date as identified in Ms. Cathie Schumaker's letter to me dated March 1, 2000. If we can provide any additional information to enable the Agency to meet this date, please contact me.

Further, if you have any questions concerning this submission, please contact me.

Very truly yours,

Wayne H. Matelski/BRW

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

Attachment

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER
20-971

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Deproco, Inc.	March 16, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
1-800-872-8305	302-328-5653
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	**AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State ZIP Code, telephone & FAX number)* IF APPLICABLE**
245-C Quigley Blvd. New Castle, DE 19720	Wayne Matelski, Esq. Arent Fox Kintner Plotkin & Kahn 1050 Connecticut Avenue, N.W. Washington, DC 20036-5339 Ph: 202-857-6340 F: 202-857-6395

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-971

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Reference Attachment	Septanest^{R} 1:100,000 and Septanest^{R} 1:200,000

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* N/A

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION:
olution for injection	Reference Attachment	Nerve block of infiltration

(PROPOSED) INDICATION(S) FOR USE:
For infiltration or nerve block anesthesia for dentistry

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

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Name of Drug N/A Holder of Approved Application

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REASON FOR SUBMISSION Response to FDA Questions

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

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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X	19. OTHER (Specify) Response to FDA Questions

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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.
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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
Wayne H. Matelski/BTW	Wayne Matelski, Esq. U.S. Agent	3/16/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1050 Connecticut Avenue, N.W. Washington, DC 20036-5339	(202) 857-6340

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

HHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

Attachment to FDA 356h
NDA 20-971

Established Name(s)

Septanest ® 1:200,000 Articaine Hydrochloride 4% with Epinephrine 1:200,000
Septanest ® 1:100,000 Articaine Hydrochloride 4% with Epinephrine 1:100,000

Strengths
Articaine Hydrochloride 4% with Epinephrine 1:100,000 or 1:200,000

Cross-References

Drug Master Files (DMFs)

DMF
DMF
DMF
DMF
DMF
DMF
DMF

Establishment Information

The drug product is manufactured by

Specialites Septodont
58, rue du Pont de Creteil
Saint-Maur-Des-Fossés
94100 Paris
France

The manufacturer of

The manufacturer of

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Arent Fox
ATTORNEYS AT LAW

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1050 Connecticut Avenue, NW Washington, DC 20036-5339
Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Wayne H. Matelski
Direct 202/857-6340
matelskw@arentfox.com

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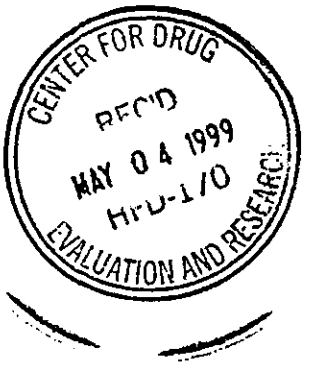
ORIG AMENDMENT
ORIGINAL



BY HAND DELIVERY

May 4, 1999

Dr. Susmita Samanta
Division of Anesthetic, Critical Care, &
Addiction Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
Response to Request for Information Concerning Cartridge Labeling

Dear Dr. Samanta:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am responding to your request for information concerning the labeling of Septanest® cartridges. In the FDA's Approvable Letter dated January 29, 1999, the Agency requested assurance that the imprinting on the cartridges would not rub off with normal use. In the Sponsor's Response to the Approvable Letter, dated March 9, 1999, the Sponsor described the [redacted] process it intended to use to ensure that the printing would not rub off during normal use. On April 28, 1999, you contacted us by telephone and requested additional information on the imprinting process.

In response to your request, we have attached the following:

1. A statement prepared by the Jacques Barrière, Industrial Manager, Spécialités Septodont, describing the company's switch from a [redacted] process for cartridge imprinting to an [redacted] process. (Attachment 1)

2. A letter from [redacted] to Spécialités Septodont, describing the [redacted] process used by [redacted] to imprint cartridges. (Attachment 2)

3. Five (5) samples of cartridges imprinted using the [redacted] process. (Attachment 3) As you will see, the imprinting is securely affixed to the cartridges and will not rub off under normal conditions of use.

I trust that this information addresses your concerns. If you have any additional questions, please do not hesitate to contact me.

Thank you for your assistance.

Very truly yours,

Wayne H. Matelski

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

Attachments

Spécialités Septodont
58, rue du Pont de Créteil
94107 Saint-Maur-des-Fossés Cedex
Tél.: 01 49 76 70 00
Fax: 01 48 85 54 01
Télex 264 489 F Septodt

RE : Printing of the cartridges for the US market.

Until the end of January 1999, the cartridges for the US market were either in-house [redacted] or [redacted]

The [redacted] operation consists in a printing which sometimes rubs off during subsequent operation.

Conscious of this problem, Septodont stopped the in-house [redacted] operation for US and now only uses [redacted] cartridges.

The [redacted] consists in a printing which is [redacted] and is wear resistant.

Saint-Maur-des-Fossés, April 29, 1999

Industrial Manager
J. BARRIERE

Redacted 1

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TELEFACSIMILE TRANSMITTAL FORM
FAX NUMBER: [redacted]

DATE: 1/15/99

TO: Ken Nolan ***FROM:*** [redacted]

TELEFAX #: [redacted]

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 1

NOTE: *If you do not receive the correct number of pages or if the transmission is unclear, please call* [redacted]

MESSAGE: (if any):

Per our telephone conversation on 1/14/99, the meeting requested by [redacted] regarding DMF [redacted] has been withdrawn.

OFFICIAL

JAN 13 1999

COVER SHEET

FAX

To: Wayne Matelski and Brian Waldman
Fax #: 202-857-6395
Subject: NDA 20-971 (Deproco) Septanest
Date: January 13, 1999
Pages: 1, Not including this cover sheet.

COMMENTS:

Brian:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest (Articaine Hydrochloride 4% with Epinephrine 1/200,000 solution for injection) and Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We also refer to your facsimile dated January 12, 1999 and the January 8, 1999 telephone conversation between you and Ken Nolan.

During our January 8, 1999 telephone conversation regarding NDA 20-971 (Deproco) Septanest, it was requested that you provide clarification as to whether the printing ink used for the exhibit samples submitted to the Agency will be similar to marketed drug product. Your January 12, 1999 facsimile notes that the [redacted] used in the sample will be similar to the marketed product. However, your correspondence does not state whether the printing ink used on the sample will be identical to marketed drug product.

We have noted that upon removing the glass cartridges from the outer plastic packaging the printing was not legible in places. It is not clear whether this was due to a problem during the printing process or to deterioration after printing.

Please clarify whether the printing ink and the process used to manufacture the sample will be used in manufacturing the marketed drug product. Also, please address the matter of illegible printing on the glass cartridges.

If you have any questions regarding this matter, please contact Ken Nolan at 301-827-7410.

Sincerely,

/S/

2 HD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170

TRANSMISSION RESULT REPORT (JAN 13 '99 05:43PM)

DACCADP HFD 170

(AUTO)

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FILE	FILE TYPE	OPTION	TEL NO.	PAGE	RESULT
047	TRANSMISSION		92028576395	02	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

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FACSIMILE TRANSMITTAL COVER SHEET

INFORMATION

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: January 12, 1999

No. of Pages: 3
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. Ken Nolan '99	301/~~443-7068~~ 480-8682	301/827-7411

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

Second try to a different #.

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Transmitting From: 202/857-6395

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Ave., N.W. Washington, D.C. 20036-5339

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ATTORNEYS AT LAW

Brian P. Waldman

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Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Direct 202/857-8971
waldmanb@arentfox.com

BY FAX

January 12, 1999

Mr. Ken Nolan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971
Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720

Dear Ken:

This fax confirms my voice-mail message to you of earlier today concerning product packaging for Septanest® products (NDA 20-971). In a telephone discussion on January 8th, you asked whether the samples of Septanest® submitted to the Agency utilized the same [redacted] that the Sponsor intends to use in the marketed product. As I noted in my voice-mail message, the Sponsor confirmed that the [redacted] utilized in the samples are the same as those described in the NDA and the same as those intended to be used with the marketed product. As I mentioned in our discussion on January 8th, it is important to note that the Sponsor submitted an Amendment to the NDA on October 23, 1998, seeking approval of a second type of seal.

As you requested, we have asked [redacted] to send you a copy of its 483 response which, we understand, will contain a section addressing the manufacture of [redacted] and [redacted] commitment to be available for an inspection by February 28, 1999. We further understand that [redacted] intends to submit its response tomorrow.

Finally, as we discussed in our conversation on January 6, please let me know at your earliest possible convenience whether you have been able to discuss with Dr. McCormick whether she would agree to approve the NDA without a preapproval inspection of [redacted] As explained in Wayne Matelski's letter of December 24, 1998, to Dr. McCormick, the Sponsor believes that

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such an inspection may not be necessary because of the safety controls already in place in the manufacture of the finished drug product.

I look forward to hearing from you.

Sincerely,

B P. Waldman

Brian P. Waldman
Counsel to Spécialités Septodont
and Deproco, Inc.

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

From:
Wayne H. Matelski
Tel: 202/857-6340
Fax: 202/857-6395
E-mail: mateiskw@arentfox.com

Date: December 24, 1998

No. of Pages: 4
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Dr. Cynthia McCormick	301/443-7068	301/827-7410
Mr. Ken Nolan		301/827-7411

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

Please Call As Soon As Possible If Transmission Is Not Complete: 202/857-6119
Transmitting From: 202/857-6395

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Wayne H. Matelski

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Direct 202/857-6340
matelskw@arentfox.com

BY FAX

December 24, 1998

Dr. Cynthia McCormick
Division Director
Division of Anesthetic, Critical Care, & Addiction Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
INSPECTION OF [redacted]

Dear Dr. McCormick:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am following up on our recent conversations concerning the availability of [redacted] (the DMF-holder [redacted]) for a preapproval inspection. We have now received a commitment from [redacted] and I wanted to share this information with you.

According to Mr. [redacted], the company will be ready for a preapproval inspection by February 28, 1999. We are, of course, extremely disappointed that [redacted] will not be ready before then, but remain hopeful that the Agency will consider approving the NDA without inspecting [redacted] facility. Let me briefly explain the basis upon which we believe an inspection may not be necessary.

As you may know, during the FDA's inspection of [redacted] earlier this month, [redacted] asked the Agency not to review the [redacted] facility as part of the formal inspection. [redacted] did, however, seek and obtain comments from the FDA inspector concerning the existing

_ facility and the company's planned upgrades. After the inspection, the FDA inspector issued a Form FDA-483 which, according to Mr. [redacted], identified a number of Observations concerning the company's non _ facilities. [redacted] intends to submit a response to the 483 during the second week in January and, again according to Mr. [redacted] the response will contain a section specifically discussing [redacted] plans and commitments concerning the _ facility. [redacted] is hopeful that its response will obviate the need for a follow-up inspection of either its non- ; or the _ facilities. If this is the case, we would hope that you could approve the NDA without a preapproval inspection.

During our December 3 teleconference, I asked whether the Agency would consider approving the NDA prior to the inspection of [redacted] _ facility. Although you noted that you did not think the Agency would approve the NDA until after such an inspection, you agreed to consider this request. We are hopeful that [redacted] response in January, when considered together with the controls Spécialités Septodont currently relies upon to ensure the safety of the drug substance ( ) and the drug product[1], will enable the Agency to approve the NDA without a preapproval inspection of [redacted]

I will call you, through Mr. Nolan, during the first week in January to share any additional information [redacted] may provide to us and to discuss this matter further.

---

[1] As I summarized during the December 3 teleconference, Spécialités Septodont incorporates numerous controls in the manufacturing process to ensure safety, including:

- In addition to requiring a certificate of analysis from [redacted] for each batch of articaine, Spécialités Septodont conducts its own analyses on each batch to ensure that product specifications are met. All tests identified on the [redacted] certificate of analysis are also conducted by Spécialités Septodont.
- Spécialités Septodont conducts bacterial endotoxin tests as part of its finished drug product specifications.
- Spécialités Septodont's manufacturing process includes [redacted]

Further, Spécialités Septodont would be willing to conduct bioburden and endotoxin analyses on each batch of articaine received from [redacted] if requested to do so by the Agency.

Thank you for your assistance. Happy Holidays.

Very truly yours,

Wayne H. Matelski/FW

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

cc: Ken Nolan

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

COPY FOR YOUR INFORMATION

FROM:
Wayne H. Matelski
Tel: 202/857-6340
Fax: 202/857-6395
E-mail: matelskw@arentfox.com

Date: December 1, 1998

No. of Pages: 3
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. Ken Nolan	301/480-8682	301/827-7411

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

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Transmitting From: 202/857-6395

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Wayne H. Matelski

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Direct 202/857-6340
matelskw@arentfox.com

BY FAX

December 1, 1998

Mr. Ken Nolan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
REQUEST FOR TELECONFERENCE

Dear Mr. Nolan:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am following up on your recent conversations with Brian Waldman concerning the Sponsor's request to meet with you, Dr. McCormick, and Dr. D'Sa regarding the Agency's inspection of [redacted] the DMF-holder for [redacted] in support of NDA 20-971. While Mr. Waldman originally requested a meeting with you — as opposed to a teleconference — we understand that a teleconference would be preferable from the Agency's standpoint. Therefore, we would now like to request a teleconference with you for Thursday or Friday.

As Mr. Waldman mentioned, we would like to share with you the results of our discussions with [redacted] management regarding the scheduled inspection. While we are still working out the details with [redacted] it appears at this point that [redacted] will not be ready for an FDA inspection in December. The Sponsor has taken some steps, and is willing to take additional steps, however, that may obviate the need for a pre-approval inspection of the [redacted] facility. We would like to discuss with you these measures that are designed to ensure the safety of the drug substance and the finished drug product.

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Please let me know at your earliest possible convenience whether you are available for a teleconference later this week.

Thank you for your assistance.

Very truly yours,

Wayne H. Matelski/BW

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

TRANSMISSION RESULT REPORT (DEC 01 '98 12:38PM)

DACCADP HFD 170

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FILE	FILE TYPE	OPTION	TEL NO.	PAGE	RESULT
066	TRANSMISSION		76776	18	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

Ken

cpi Sivertis
Bob
D'SA
McCormick
11/24/98

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: November 24, 1998

No. of Pages: 1
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. David Morgan	301/443-7068	301/827-7410
Mr Ken Nolan		301/827-7411

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

Dear Mr. Morgan:

This fax follows up on my voice-mail message to you this morning concerning the inspection of [redacted] the DMF-holder for [redacted] in support of the approval of NDA 20-971. As I noted, the Sponsor and [redacted] are continuing their discussions to determine whether the FDA will be able to conduct its inspection in December. We expect to have additional information from [redacted] within the next few days and will contact you early next week with an update.

Please call with any questions.

Best regards,
Brian Waldman

15:19 24 NOV 98.

cc. Ken Nolan
Wayne Matelski

Please Call As Soon As Possible If Transmission Is Not Complete: 202/857-6119
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FACSIMILE TRANSMITTAL COVER SHEET

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: August 20, 1998

No. of Pages: 3
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. Ken Nolan	301/443-7068	301/443-3741

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

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Direct 202/857-8971
waldmanb@arentfox.com

BY FAX

August 20, 1998

Mr. Ken Nolan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
Summary of Submissions to NDA File

Dear Ken:

This letter follows up on our conversation on August 17 concerning the Sponsor's submissions to the NDA file for NDA 20-971. Because initially you were unable to locate the submission dated June 30, 1998, I agreed to provide a list of all submissions to the NDA file so that you could verify that the NDA file is complete. Set forth below is a summary of each submission.

1.	April 20, 1998:	Response to questions posed by Dr. Mathew Thomas, Division of Clinical Investigations, concerning the conduct of the pivotal trials.
2.	April 29, 1998:	Submission of: (a) a certified English translation of a German patent submitted with the NDA; and (b) international labeling (in original language as well as certified English translation) currently used for Septanest® products.
3.	May 18, 1998:	Response to your request for a new debarment certification statement and an electronic copy of the package insert.
4.	May 26, 1998:	Submission of Septanest® labeling used in Canada, including a certified English translation.

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5.	June 24, 1998:	Response to your request for an electronic version of the datasets from the Sponsor's three Phase III trials.
6.	June 30, 1998:	Response to your request for, among other things, samples of drug product, subgroup analysis by gender of the effects observed in the Sponsor's Phase II trial, subgroup analyses by race and gender of the efficacy data developed in the Sponsor's three Phase III trials, and an electronic version of the proposed labeling, the Integrated Summary of Safety, the Integrated Summary of Efficacy, and the study reports for the Sponsor's Phase II and Phase III trials.
7.	July 6, 1998:	Response to your request for sample of drug product sold in Austria and an electronic version of the datasets from the Sponsor's three Phase III trials.
8.	July 14, 1998:	Response to your request for photographs of a Septanest® cartridge in a syringe and a sample syringe.
9.	August 6, 1998:	Submission of Four Month Safety Update Report.

If you are unable to locate copies of any of these submissions in the NDA file please let me know and I will forward additional copies to your attention.

Finally, we are hopeful that the above list will facilitate your scheduling of the next internal FDA meeting to discuss the status of the NDA review. We look forward to receiving a summary of your discussions. On July 1 you noted that you intended to schedule the meeting for late July. I know that it is difficult to schedule a meeting in the summer, but we respectfully request that you schedule this meeting at your earliest possible convenience so that we may respond quickly to any issues that may be raised during the meeting.

As always, we greatly appreciate your assistance.

Very truly yours,

Brian P. Waldman
Counsel to Spécialités Septodont
and Deproco, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-971

AUG 19 1998

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Sepecialities Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We are reviewing the chemistry section(s) of your submission and have the following ten (10) comments and information requests:

1. Please provide a linkage table that correlates the following: a) clinical study protocol number b) Septanest drug product lot, and c)Articaine HCl drug substance lots.

2. Please provide certificates of analysis and executed batch records for the clinical materials used in Phase III Pivotal clinical studies S96001US (n=569), S96002 (n=155), and S96001UK (n=158).

3. We recommend specifications for enantiomeric excess, water content, and bioburden for Articaine HCl drug substance.

4. Please provide an updated stability report with the — month stability data. Please submit chromatograms at — and — month test points.

5. Overage for any product merely to extend the expiration dating is not acceptable. Therefore, please provide process validation documentation that justifies use of 15% overage for epinephrine bitartrate.

6. Please submit container labels with the distributor name imprint so as to comply with 21 CFR 201.1.

7. Pertaining to the [redacted]

a. [redacted] Please explain why validation was performed at maximum conditions. Validation for sterilization of the drug product should be carried out under worst case, at minimum process parameters or less.
b. Please provide data for the minimum temperature and minimum F_0 achieved in each validation run.

8. Pertaining to the microbiological efficacy of the sterilization cycle

a. Please provide a description on the filling and assembly of the cartridges prior to [redacted] sterilization. In particular, how are the [redacted] assembled and how is sterility of the closures maintained during assembly? Are the filling and assembly performed [redacted]?
b. Validation should be performed [redacted] It is not sufficient to use only [redacted] to validate a full load.
c. Validation should be performed [redacted] value of the [redacted] in product should be determined. It appears that the [redacted] were not inserted into the cartridges containing the drug product. What is the content of the filled cartridges? Please specify if the [redacted] were inserted into empty or filled cartridges.
d. Please explain how the survivors were determined after sterilization.
e. Validation data to demonstrate in-process container-closure integrity for the [redacted] of the drug product should be submitted for review. Validation can be performed by [redacted] and determining

9. Pertaining to microbiological monitoring of the environment

The specification limit of [redacted] cfu/mL for [redacted] is too high and should be revised. In addition, data on the microbial counts showed that there was no appreciable difference before and after [redacted] It is critical to perform validation study to demonstrate container-closure integrity [redacted] and such validation data should be submitted for review.

10. Pertaining to the container-closure integrity

a. Are the media filled cartridges subjected to [redacted] prior to the microbial immersion test? If not, please provide an explanation.
b. Please explain why it is necessary to change to [redacted]

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. In accordance with the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Ken Nolan, Project Manager, at 301-443-3741.

Sincerely,

/S/ ... MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

TRANSMISSION RESULT REPORT (AUG 19 '98 04:37PM)

DACCADP HFD 170

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FILE	FILE TYPE	OPTION	TEL NO.	PAGE	RESULT
042	TRANSMISSION		92028576395	04	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

FAX TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
OFFICE: 301-443-4250/3741
FAX: 301-443-7068/480-8682

TO: Dr. Chuanpu Hu
15B-45

DATE: 7-13-98

FAX #: 7-3213

PAGES: 4
(INCLUDING THIS COVER SHEET)

FROM: Kenneth Nolan

SUBJECT: NDA 20-911

COMMENTS:

Forwarding by Ken's request on 7-9-98 e-mail.

PLEASE CALL (301) 443-4250 or 443-3741 IF RE-TRANSMISSION IS NECESSARY

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: July 10, 1998

No. of Pages: 3
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. David Morgan	301/443-7068	301/443-3741

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

APPEARS THIS WAY ON ORIGINAL

Please Call As Soon As Possible If Transmission Is Not Complete: 202/857-6119
Transmitting From: 202/857-6395

Arent Fox
ATTORNEYS AT LAW

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW Washington, DC 20036-5339
Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Brian P. Waldman
Direct 202/857-8971
waldmanb@arentfox.com

BY FAX

July 10, 1998

Mr. David Morgan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971
Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
Response to Request for Clarification

Dear Mr. Morgan:

This letter follows up on my telephone conversation yesterday with Mr. Ken Nolan and Dr. Chuanpu Hu concerning electronic datasets we submitted to the Agency on behalf of the Sponsor. Ken asked me to forward this letter to you because he is out of the office today.

During our conversation yesterday, Dr. Hu indicated that he could not open some of the files we had submitted on diskette. Dr. Hu requested that we provide a written explanation describing how he could open those files with an .XPT extension in a readable format.

In response to Dr. Hu's request, I contacted the Sponsor's ——— ——— the company that prepared the datasets. ——— explained to me that the diskettes provided to the Agency contain SAS datasets. The data reside in files called ———. ——— These are self-extracting files that must first be moved from the diskette to the directory on the computer where the resultant files will reside. At the DOS prompt, the reviewer should type ——— ———, respectively, to extract the files. As Dr. Hu noted, this will create several files with the .XPT extension. These are SAS transport format files containing SAS datasets.

The following SAS LIBNAME statements then should be used to tell SAS where the transport format file resides:

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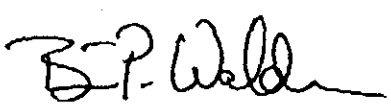
Finally, the reviewer must use a FILENAME statement to bring the particular dataset into the SAS program.

Please note that the diskettes submitted also include a file called ———— ; that contains PROC CONTENTS for each dataset and a PROC PRINT of the first fifty (50) observations for each dataset.

I am hopeful that this response will adequately address Dr. Hu's questions. Of course, if he would like additional information, please contact me.

Thank you for your assistance.

Sincerely,



Brian P. Waldman
Counsel to Spécialités Septodont
and Deproco, Inc.

TRANSMISSION RESULT REPORT (JUL 13 '98 10:31AM)

DACCADP HFD 170

(AUTO)

THE FOLLOWING FILE(S) ERASED

FILE	FILE TYPE	OPTION	TEL NO.	PAGE	RESULT
065	TRANSMISSION		75210	04	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

Arent Fox
ATTORNEYS AT LAW

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Brian P. Waldman

Direct 202/857-8971
waldmanb@arentfox.com

BY FAX

June 18, 1998

Mr. Ken Nolan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-971**
Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
Schedule for Submitting Response to Request for Additional Information

Dear Ken:

This letter follows up on our telephone conversation on June 16 during which you responded to our request for clarification concerning the FDA's most recent request for additional information. Specifically, you clarified Dr. Chuanpu Hu's request for subgroup analyses of the efficacy data developed by the Sponsor.

In our earlier conversations, I had stated that we would be able to submit our response to the FDA's request on June 22. In our June 16 conversation, after you clarified Dr. Hu's request, I stated that our response might be delayed because we would have to generate additional materials to respond fully to Dr. Hu's request. You suggested that if we would not be able to submit our response by June 22, that I send a letter to you proposing a new submission date. After conferring with [redacted] the contract research organization assisting us in preparing our response, we have determined that we will be able to submit our response to you by June 30.

If this revised submission date is unacceptable to the FDA, please contact me at your earliest convenience.

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Thank you for your assistance.

Sincerely,

Brian P. Waldman
Counsel to Spécialités Septodont
and Deproco, Inc.

Attachment

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: June 18, 1998

No. of Pages: 3
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. Ken Nolan	301/443-7068	301/443-3741

Attorney Number: 1115 Client Number: 010026-00011

Hard Copy Sent: No

APPEARS THIS WAY ON ORIGINAL

Comments:

98 JUN 18 PM 2:26

Please Call As Soon As Possible If Transmission Is Not Complete: 202/857-6119
Transmitting From: 202/857-6395

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Ave., N.W. Washington, D.C. 20036-5339

Arent Fox
FACSIMILE TRANSMITTAL COVER SHEET

JUN 12 1998

FROM:
Brian P. Waldman
Tel: 202/857-8971
Fax: 202/857-6395
E-mail: waldmanb@arentfox.com

Date: June 12, 1998

No. of Pages: 4
(Including Cover Sheet)

PLEASE DELIVER TO:

Name:	Fax Number:	Verify Number:
Mr. Ken Nolan	301/443-7068	301/443-3741

APPEARS THIS WAY ON ORIGINAL

Attorney Number: 1115 **Client Number:** 010026-00011

Hard Copy Sent: No

Comments:

Please Call As Soon As Possible If Transmission Is Not Complete: 202/857-6119
Transmitting From: 202/857-6395

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Ave., N.W. Washington, D.C. 20036-5339

Arent Fox
ATTORNEYS AT LAW

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Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Brian P. Waldman
Direct 202/857-6971
waldmanb@arentfox.com

BY FAX

June 12, 1998

Mr. Ken Nolan
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-971**
Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
Clarification of Request for Additional Information

Dear Ken:

This letter follows up on our conversation this afternoon concerning our understanding of Dr. Hu's request for additional information. We have two requests for clarification:

1. In your June 11 fax to me (attached) summarizing our June 11 teleconference with Dr. Hu, you noted that Dr. Hu had requested:

   "3. Efficacy and safety subgroup analysis by race and gender (including SAS program code used to generate the results)."

   It was my understanding from our conversations on June 8th, 9th, and 11th that Dr. Hu wanted the subgroup analyses of the efficacy data only. Please confirm whether Dr. Hu would like the subgroup analyses for both the efficacy and safety data or just the efficacy data.

2. When we prepare the subgroup analyses -- whether for the efficacy data alone or for both the efficacy and safety data -- does Dr. Hu want us to provide the subgroup analyses for

Arent Fox

each of the three Phase III trials separately or for the single integrated efficacy (and safety) report?

As we agreed, I will call you on Monday to discuss these issues. Thank you for your assistance.

Sincerely,

Brian P. Waldman
Counsel to Spécialités Septodont
and Deproco, Inc.

Attachment

From the desk of...

KEN NOLAN
PROJECT MANAGER/CSO
CDER/ODEIII/DACCAD
HFD-170, RM 8B-45
5600 FISHERS LANE
ROCKVILLE, MD 20857
301.443.3741
Fax: 301.443.7088 OR 301.443.4835

COVER SHEET FAX

To: Brian Waldman
Fax #: 202-857-6395
Subject: NDA 20-871 Documentation of June 11, 1998 Telephone Conversation
Date: June 11, 1998
Pages: , Not including this cover sheet.

COMMENTS:

Brian:

Please refer to your New Drug Application (NDA) dated March 30, 1998, received March 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1:200,000 solution for injection) and Septanest® — (Articaine Hydrochloride 4% with Epinephrine 1:100,000 solution for injection).

We refer to the June 11, 1998 telephone conversation between you, Chuanpu Hu, Ph.D. and Ken Nolan regarding our request for statistical information. The Agency requested the items listed below regarding phase III clinical pivotal trials. It was mutually agreed the items should be submitted by June 22, 1998

1. Description of data set (i.e., explain variables names).

2. The SAS program code used to generate efficacy and safety results.

3. Efficacy and safety subgroup analysis by race and gender(including SAS program code used to generate the results).

If you have any questions regarding this matter please contact me on 301-443-3741. Should you have questions regarding this matter, please contact me promptly on 301-443-3741.

Ken Nolan
Project Manager
FDA/CDER/ODEIII/DACCAD

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Jun-1998 02:05pm EDT
From: Kenneth Nolan
NOLANK
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

TO: Chuanpu Hu (HUC)

Subject: FWD: Re: NDA 20-971 (Deproco) Articaine

Chuanpu:

I forward your attached response to the sponsor regarding the June 12, 1998 fax. The will be unable to complete the Phase III trials anaylses by June 22, 1998. I recommended that they forward a fax explaining the situation and provide a time frame when a response will be submitted. Upon receiving the fax I will forward for your reveiw.

If you have any questions please let me know.

Ken

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 13-Jun-1998 10:30am EDT
From: Chuanpu Hu
HUC
Dept: HFD-705 PKLN 15B32
Tel No: 301-827-3116 FAX 301-443-5161

TO: Kenneth Nolan (NOLANK)

Subject: Re: NDA 20-971 (Deproco) Articaine

Ken:

The answers to the questions are:

(1) The subgroup analysis by race and age for efficacy only.
(2) Subgroup analyses for each of the three Ph. III trials separately.

You are welcome to call me on Monday if you have more questions.

Chuanpu

>
>
> Chuanpu:
>
> Brian Waldman has sent a fax requesting clarification regarding:
> 1. the subgroup analysis by race and age for efficacy and safety
data
> or just the efficacy data
>
> 2. subgroup analyses for each of the three Ph. III trials
separately
> or for the single integrated efficacy (and safety) report.
>
>
>
> Please give me a call at 11:00 a.m. Monday 6-15 and I will forward
the
> faox. At that time you can let me know how to proceed in reponding.
>
> Thanks,
>
> Ken
>

From the desk of...

KEN NOLAN
PROJECT MANAGER/CSO
CDER/ODEIII/DACCAD
HFD-170, RM 9B-45
5600 FISHERS LANE
ROCKVILLE, MD 20857
301.443.3741
Fax 301.443.7068 OR 301.443.4935

COVER SHEET FAX

To: Brian Waldman and Wayne Matelski
Fax #: 202-857-6395
Subject: NDA 20-971 Debarment Certification Statement
Date: May 13, 1998
Pages: 14, Not including this cover sheet.

COMMENTS:

Brian:

Please refer to your New Drug Application (NDA) dated March 30, 1998, received March 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1:200,000 solution for injection) and Septanest® — (Articaine Hydrochloride 4% with Epinephrine 1:100,000 solution for injection).

Per our telephone conversation this morning regarding NDA 20-971 debarment certification statement, please find attached the Draft Guidance for Industry For the Submission of Debarment Certification Statements and Other Information Under the Generic Drug Enforcement Act of 1992. (Please see page 2.)

Please submit a revised debarment statement as recommended in the attached guidance document.

Should you have questions regarding this matter, please contact me promptly on 301-443-3741.

Ken Nolan
Project Manager
FDA/CDER/ODEIII/DACCAD

Guidance for Industry

DRAFT

For the Submission of Debarment Certification Statements and Other Information Under the Generic Drug Enforcement Act of 1992

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

[month] 1996

GG1

DRAFT

Table of Contents

DRAFT

GUIDANCE FOR INDUSTRY[1]

FOR THE SUBMISSION OF DEBARMENT CERTIFICATION STATEMENTS AND OTHER INFORMATION UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

I. INTRODUCTION

Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Generic Drug Enforcement Act of 1992 (GDEA) addresses the requirement on the part of drug product applicants to certify that the services of debarred persons have not been used in the drug product application.

Since the 1992 amendment, a number of inquiries have been made requesting clarification of specific aspects of that part of the act. As a result, the FDA has created this guidance to address the most common questions about the act's certification and information requirements. The information presented here is drawn from the act itself and from letters written by the FDA to address specific questions.

II. 306(k)(1) CERTIFICATION REQUIREMENTS

Section 306(k)(1) [21 U.S.C. 335a(k)(1)] of the act states that, "any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)], in connection with such application."

A. Applications subject to the certification requirements of 306(k)(1)

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[1]This guidance has been prepared by the Debarment Task Force at the Food and Drug Administration (FDA). Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the information that should be submitted to satisfy the requirements of the Generic Drug Enforcement Act of 1992. For additional copies of this guidance, contact the Drug Information Branch, Division of Communications Management (HFD-210) CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012), the Manufacturers Assistance and Communication Staff (HFM-42), CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448 (Phone: 301-827-2000), or the Communications and Education Branch (HFV-12), CVM, FDA, 7500 Standish Place, Rockville, MD 20855 (Phone: 301-594-1755). Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW) (connect to the CDER Home Page at WWW.FDA.GOV/CDER and go to the "Regulatory Guidance" section.). A copy of the document may also be obtained via FAX by calling the CBER Voice Information System at 1-800-835-4709 or via "bounce-back" e-mail by sending a message to "GDEGEN@A1.CBER.FDA.GOV."

The following drug product applications received by the FDA on or after June 1, 1992, should submit a certification statement:

- New drug applications (NDAs)
- Abbreviated new drug applications (ANDAs)
- Antibiotic drug applications
- Abbreviated antibiotic applications (AADAs)
- New animal drug applications (NADAs)
- Abbreviated new animal drug applications (ANADAs)
- Export applications for certain unapproved products
- Biological product license applications (PLAs)
- Supplements to certain drug product applications.

B. Wording of the certification statement

The FDA regards the following wording, taken from section 306(k)(1) of the act (21 U.S.C. 335a(k)(1)), as the most acceptable form of certification:

> *[Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the act, in connection with this application.*

Use of conditional or qualifying language, such as *to the best of my knowledge*, is unsatisfactory.

NADA and ANADA applicants should simply sign the standard certification form 356-V provided by the agency, which contains the preferred language for certification.

C. Persons covered by the certification

To obtain approval, the drug product applicant is asked to certify that no person whose services were used in any capacity in connection with . . . [the] application, including any persons with the ability to exercise control over persons performing such services, is debarred. Under the act, the term *person* includes an individual, partnership, corporation, and association. The agency defines *services* in connection with . . . [the] application to include any services related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application. Persons whose services were used in any capacity in connection with the application include, but are not limited to, the following:

- Employees of the applicant
- Certain contractors and their employees (e.g., contract research organizations

whose studies were used in the application)

- Certain subcontractors and their employees (e.g., consultants hired by a contract research organization)
- Clinical investigators
- Persons contributing data and information contained in a drug master file (DMF) or public master file (PMF), incorporated by reference in the application

D. Basis of certification

To certify correctly, the applicant may check its list of employees and other persons with whom it does business against the list of debarred persons. This list is available upon written request from the Division of Compliance Policy (HFC-230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

The applicant also may request and rely on certification statements from employees, contractors, subcontractors, clinical investigators, DMF or PMF holders, and the employees of such persons unless the applicant acts in deliberate ignorance of or reckless disregard for the truth or falsity of the information. The DMF or PMF holder may include a certification in the DMF or PMF, thereby allowing all referencing applicants to rely on that one certification, or the DMF or PMF holder may provide a separate certification to each applicant. The applicant's certification includes all persons who have contributed data or information related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application, regardless of whether such persons submit certifications directly to the FDA or to the applicant.

Because the statutory language of the certification statement is both retrospective and prospective (i.e., the applicant did not and will not use in any capacity the services of any person debarred in connection with the application), the applicant need not inquire again and again to obtain updated written statements from employees, contractors, and others, unless there is reason to believe that the original certification statement is incorrect or that the applicant has used, in connection with the application, amendment, or supplement, the services of a person not used in the previous submission. In such instances, the applicant has an ongoing duty to use due diligence to ensure the continued correctness of the certification.

E. Supplements

Only supplements to ANDAs and AADAs that provide for a *different or additional* use of the drug should contain a certification. Supplements to other drug product applications need not contain a certification.

Supplements providing for a *different or additional use* of the drug are limited to those that provide for a new use (1) not covered by the listed drug and (2) supported by clinical data (i.e., a supplement providing for a new indication, dosage form, or strength that requires supporting clinical data). Under this interpretation, only applications submitted under 21 CFR 314.54 and AADA supplements providing for a use not covered by the reference antibiotic drug and supported by clinical data should submit a certification.

For example, a supplement to an ANDA or AADA that improves the formulation or manufacturing process, or changes ingredient suppliers, or proposes other production changes not requiring clinical data does not require certification. Also, a supplement to an ANDA or an AADA that adds an indication to the labeling of the generic drug because exclusivity has expired for that indication need not contain a certification.

F. Scope of debarment

The act states that a drug product applicant may not use in any capacity the services of a debarred person. The agency has interpreted services in any capacity to mean any service provided to the drug applicant, whether or not related to drug regulation. That means a debarred individual may not provide nondrug related services to a drug product applicant (e.g., as a landscaper, a computer software supplier, an accountant, a telephone repair person, a janitor, an interior decorator, a landlord, etc.) without violating debarment. Both the firm and individual are subject to substantial civil penalties for violation of this provision.

G. Scope of certification

The scope of certification is narrower than the scope of debarment. The act states an applicant should certify that it did not and will not use in any capacity the services of a debarred person, *in connection with such application*. Thus, the applicant should certify only with regard to any services received in connection with the application, that is services related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application. Persons included in the definition may encompass, for example, the applicant's own employees, contractors (e.g., a contract research organization used to run a study), subcontractors (e.g., a special consultant hired by a contract research organization), clinical investigators, DMF or PMF holders, and employees of such

persons, regardless of whether foreign or domestic, if the services provided were related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application.

Thus, an applicant using the services of a debarred person may still certify properly, so long as the services provided by the debarred person are not related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application. However, under the act, both the applicant using the services of a debarred person in any capacity and the debarred person are subject to substantial civil money penalties for violation of debarment.

H. Limitations on stock ownership of debarred persons

A debarred person may own stock in a firm that has an approved or pending drug product application, but may not participate in any capacity in business decisions or operations of such a firm (e.g., participating in shareholder voting) without violating debarment.

In addition, if a debarred person exercises any control over business decisions or operations of a firm that has an approved or pending drug product application, for example, via shares owned by someone other than the debarred person (i.e., any member of the debarred person's family, or any other individual, partnership, corporation, or association), the FDA will regard the debarred person as providing services to a drug product applicant in violation of debarment. In such instances, both the firm and the debarred person would be subject to substantial civil money penalties for violation of debarment.

I. Domestic agents

Domestic agents should countersign the certification for foreign applicants they represent under 21 CFR 314.50(a)(5).

J. Investigational drugs

Applications for investigational drugs (IND) described under 21 CFR 312.40 (INDs), 21 CFR 312.110(a) (import INDs), 21 CFR 312.110(b) (export INDs), or 21 CFR 511.1 (INADs) do not require a certification statement because INDs and INADs are not considered drug product applications under the GDEA. INDs and ANADs are submitted for the purpose of clinical research. However, it should be noted that the certification required in a drug application for approval (e.g., an NDA) precludes the use of a debarred person in connection with any IND associated with that application.

K. Over the counter (OTC) monograph drugs

The certification requirement applies to any application for approval of a drug product. A monograph is *not* an application and, thus, drugs marketed under the conditions of an OTC monograph are not subject to the certification requirement.

L. Establishment license applications

Although establishment license applications (ELA) are subject to regulation under section 351 of the Public Health Service Act (42 U.S.C. 262), they do not require certification because ELAs are not applications for approval of a drug product as defined by that act. However, upon submission of an application for approval of a biological drug product (i.e., a PLA), an applicant would be asked to certify that no debarred person was used in connection with the application. This certification, if truthful, would preclude the use of a debarred person in connection with the establishment.

M. Debarment status

If the services of a debarred person were used in connection with the application prior to debarment or after termination of debarment, a firm could still properly certify because the person was not debarred at the time his or her services were rendered. However, data generated by a person prior to the person's debarment, or data generated after termination by a formerly debarred person, may be subject to closer examination by the agency. Therefore, it is recommended that the applicant should inspect such data to ensure that no data integrity concerns exist.

III. 306(k)(2) CONVICTION INFORMATION REQUIREMENTS

Section 306(k)(2) [21 U.S.C. 335a(k)(2)] of the act states that "any application for approval of a drug product shall include . . . if such application is an abbreviated drug application, a list of all convictions, described in subsections (a) and (b) [section 306(a) and (b)] which occurred within the previous 5 years, of the applicant and affiliated persons responsible for the development or submission of such application."

A. Applications subject to the conviction information requirement

The act requires that ANDAs and AADAs, and supplements to ANDAs and AADAs submitted on or after June 1, 1992, providing for a *different or additional use*, contain a list of all convictions (occurring within the five years for which a person can be

debarred[2]) of the applicant and affiliated persons responsible for the development or submission of such application.

The section 306(k)(2) requirement for conviction information in ANDA and AADA in supplements for a *different or additional* use is limited to those supplements that provide for a new use (1) not covered by the listed drug and (2) supported by clinical data (i.e., supplements providing for a new indication, dosage form, or strength that requires supporting clinical data). Under this interpretation, only applications submitted under 21 CFR 314.54 and AADA supplements providing for a use not covered by the reference antibiotic drug and supported by clinical data should submit conviction information.

Note that a supplement to an ANDA or an AADA that adds an indication to the labeling of the generic drug because exclusivity has expired for that indication need not contain conviction information. A supplement to an ANDA or AADA that improves the formulation or manufacturing process, changes ingredient suppliers, or proposes other production changes does not require conviction information, unless the supplement contains clinical data.

B. Definition of an affiliated person

An affiliated person for whom an applicant for approval of an ANDA or AADA should provide conviction information includes any individual, partnership, corporation, or association, including employees thereof, involved with development or submission of data that (1) are used to obtain approval of an application and (2) relate to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s).

The ANDA and AADA applicant should provide conviction information for persons falling within the scope of this definition. Generally, the conviction information provided by an applicant for approval of an ANDA and AADA pertains to employees of the applicant, contractors, subcontractors, and so on, responsible for the development or submission of the abbreviated application because such persons are within the meaning of *affiliated person*. Some examples follow.

1. Secretaries

If the secretary merely transcribes data, the secretary is not regarded as an

[2]In section 306(a) and (b), Congress describes types of convictions that fall under the scope of the debarment provisions in very broad terms. Therefore, the FDA cannot provide a definitive list of such offenses or a list of all individuals and businesses with convictions for such offenses.

affiliated person within the intended definition of the act. In rare instances, the secretary may develop data used to obtain approval; in such cases that secretary is an affiliated person.

2. Clinical investigators, nurses, technicians, and other parties involved with the development or submission of data related to clinical studies (affiliated persons)

3. Janitors, packers, production crew, and assembly persons

So long as these persons do not develop or submit data, they are not affiliated persons

4. CGMP record keepers

Because the FDA reviews CGMP records when determining whether to grant or continue approval of a drug product, persons who develop and record CGMP data related to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s) are affiliated persons. (See 1992 Guidance Letter, p. 3.)

5. Commercial manufacturing facility workers

Such persons are affiliated persons if they are involved in the development or submission of records or data that are used to obtain and maintain approval of an application and relate to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s). For example, persons recording and generating data solely for the approved commercial product are affiliated persons because FDA reviews such records in determining whether to grant or continue approval of a drug product.

6. Persons working on drug master files (DMFs) or public master files (PMFs)

Persons recording and generating data for DMFs or PMFs that are relied on to support approval and that relate to the manufacturing, processing, or testing of the active ingredient(s) or finished dosage form(s), come within the definition of *affiliated person*. Persons recording and generating DMF or PMF data solely for nonchemical components (i.e., bottles or inactive ingredients) are not subject to the conviction information requirements.

C. Contents of conviction information

The list of convictions should include the following information:

- The name(s) of the convicted persons(s)
- The title and section of the Federal or State statute involved
- The date of the conviction (for which a person can be debarred, as described in section 306(a) and (b), that occurred within 5 years before the date of the application)
- The date of sentencing
- The court entering judgment
- The case number, if known
- A brief description of the offense
- The role of the person in the development or submission of the application
- The time period of the person's involvement in the development of the application

D. Basis of conviction information

Background checks are not necessary. The applicant may request and rely on conviction information received from the applicant's affiliated persons unless the applicant acts in deliberate ignorance of or reckless disregard for the truth or falsity of the information.

Under the act, conviction information is required for persons no longer working for the firm, but who were affiliated persons involved with the development or submission of the application. However, if the applicant cannot ascertain conviction information for all affiliated persons because of unavailability of the person(s), the FDA will accept the names and job titles of such people (including a description of the responsibilities that person had concerning the application) together with an explanation of the circumstances surrounding the unavailability of the person (e.g., death, or the person no longer works for the firm and reasonable efforts to locate the person have proven unsuccessful) and a statement that the applicant has no knowledge that the person has been convicted of any offense(s) for which a person can be debarred.

E. Effect on review process

If the conviction information provided raises a question concerning the integrity of the data or information contained in the application, the application may be subject to closer agency scrutiny.

IV. 306(k) CERTIFICATION AND CONVICTION INFORMATION REQUIREMENTS

A. Amendments to pending drug product applications

So long as the original application contains the requisite statement of certification and/or conviction information, there is no need to resubmit such statements in amendments described under 21 CFR 314.60(a). However, the applicant has an ongoing duty to use due diligence to assure the continued correctness of the certification. Therefore, if the original statement becomes incorrect (i.e., the applicant has used the services of a debarred or convicted person not used in the previous submission), the applicant has a responsibility to correct the certification and/or conviction information in the amendment or as soon as possible.

B. Effective date of certification and conviction information requirements

Drug product applications, including certain supplements submitted on or after June 1, 1992, are subject to the certification and/or conviction information requirements.

C. Placement in the application

The certification and/or conviction information should appear at the beginning of the application and be clearly identified. The applicant may indicate the placement of the information in the table of contents. In the case of an NADA or ANADA, a standard certification form 356-V is provided by the agency and, thus, the placement of the certification statement in such applications is already established.

D. Missing or incorrect information

If a drug product application, amendment, or supplement submitted on or after June 1, 1992, lacks or contains incorrect certification or conviction information, the applicant should amend the application, amendment, or supplement to include or correct the certification or conviction information as soon as possible. (Since February 25, 1993, the FDA has not accepted for filing ANDAs and AADAs that do not contain certification and conviction information.) The applicant has an ongoing duty to ensure that the certification or conviction information is correct.

E. Signature

The certification and/or conviction information should be signed by a responsible officer of the applicant or by the individual responsible for signing the application.

V. REFERENCES

The Generic Drug Enforcement Act of 1992, section 306 (21 U.S.C. 335a).

July 27, 1992, guidance letter from FDA's Deputy Commissioner for Operations.

May 5, 1994, letter from FDA Regulatory Counsel for the Office of Generic Drugs, CDER.

April 8, 1994, letter from FDA's Acting Director for the Office of Generic Drugs, CDER.

January 15, 1993, letter from FDA's Director for the Office of Generic Drugs, CDER.

TRANSMISSION RESULT REPORT (MAY 13 '98 11:10AM)

DACCADP HFD 170

(AUTO)

THE FOLLOWING FILE(S) ERASED

FILE	FILE TYPE	OPTION	TEL NO.	PAGE	RESULT
024	TRANSMISSION		92028576395	15	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

FAX TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
OFFICE: 301-443-4250/3741
FAX: 301-443-7068/480-8682

TO: MATHEW THOMAS

DATE: 4/7/98

FAX #: 301-594-1264

PAGES: 9
(INCLUDING THIS COVER SHEET)

FROM: KEV NAIR

SUBJECT: NDA 20-971 INVESTIGATORS INFO

COMMENTS:

PLEASE CALL (301) 443-4250 or 443-3741 IF RE-TRANSMISSION IS NECESSARY

Redacted 9

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TRANSMISSION RESULT REPORT (APR 07 '98 07:04PM)

DACCADP HFD 170

(AUTO)

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079	TRANSMISSION		93015941204	10	OK

ERRORS

1) HANG UP OR LINE FAIL 2) BUSY 3) NO ANSWER 4) NO FACSIMILE CONNECTION

Arent Fox
ATTORNEYS AT LAW

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW Washington, DC 20036-5339
Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Wayne H. Matelski
Direct 202/857-6340
matelskw@arentfox.com

BY FAX

April 3, 2000

Document Room 9B-23
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Articaine Hydrochloride 4% with Epinephrine
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
LABELING

Dear Madam/Sir:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of the proposed dental anesthetics, I am following up on my conversation this morning with Ms. Laura Governale and Dr. Robert Rappaport. During an earlier conversation on March 31, the FDA had requested that the Sponsor include the phrase "Store at 20-25°C" on the cartridge labels. Due to space limitations on the cartridge label, the Sponsor seeks a waiver from the FDA's request. I understand from the conversation this morning that such a waiver would be granted.

If you have any questions or comments concerning this submission, please contact me.

Very truly yours,

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Deproco, Inc.
c/o Arent Fox Kintner Plotkin & Kahn
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

MAR 2 0 2000

Attention: Wayne Matelski, Esq.

Dear Mr. Matelski:

Please refer to the meeting between representatives of your firm and FDA on March 16, 2000. The purpose of the meeting was to relay labeling changes to the package insert.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

/S/

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Printed from DFS

NDA 20-971

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Attention: Wayne H. Matelski, Esq.
U.S. Agent for and counsel to Specialites Septodont and Deproco, Inc.

Dear Mr. Matelski:

Please refer to the telephone conference between yourself and FDA on May 5, 1999. The purpose of the meeting was to discuss the outstanding issues that were still pending for the New Drug Application for Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000).

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

/S/

Corinne Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA 20-971
HFD-170/General Correspondence Files
HFD-170/SS/C. Moody
HFD-170/ C. McCormick
HFD-170/ B.Rappaport
HFD-820/J.Gibbs/S.Koepke
HFD-170/A.D'Sa/P.Maturu
HFD-170/H.Blatt

Drafted by: SS/June 4, 1999
Initialed by: C.P.Moody/June 4, 1999
final:
filename: 20971.mm.55

GENERAL CORRESPONDENCE (MINUTES SENT)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

JAN 13 1999

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialitie's Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest [redacted] 4% with Epinephrine 1/200,000 solution for injection) and Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We refer to the teleconference between representatives of your firm and FDA on December 18, 1998.

A copy of our minutes of that teleconference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Ken Nolan, Consumer Safety Officer, at (301) 827-7410.

Sincerely,

/S/

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-971

Food and Drug Administration
Rockville MD 20857

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

JAN 12 1999

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialitie's Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest (Articaine Hydrochloride 4% with Epinephrine 1/200,000 solution for injection) and Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We acknowledge receipt of your submission dated March 30, 1998.

We refer to the teleconference between representatives of your firm and FDA on December 3, 1998.

A copy of our minutes of that teleconference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Ken Nolan, Consumer Safety Officer, at (301) 827-7410.

Sincerely,

/S/

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA 20-971
HFD-170/Div. files
HFD-170/CMcCormick
HFD-170/BRappaport
HFD-170/HBlatt
HFD-170/Goheer
HFD-170/DJean
HFD-170/PMaturu
HFD-170/AD'Sa
HFD-705/Hu
HFD-170/TPermutt
HFD-170/MKlein
HFD-170/Uppoor
HFD-170/CMoody
HFD-44/TAbrams/Klein
HFD-324/MThomas

Drafted by: KEN/n:\cso\nolan\n20971mm.d03\\Rev.\12-21-98\Moody-ken//Rev./December 22, 199/D'Sa
Initialed by:
final:

GENERAL CORRESPONDENCE (MINUTES SENT)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 20 1999

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialitie's Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest (articaine hydrochloride 4% with Epinephrine 1/200,000 solution for injection) and Septanest (articaine hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We refer to the teleconference between representatives of your firm and FDA on November 13, 1998.

A copy of our minutes of that teleconference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Ken Nolan, Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Arent Fox
ATTORNEYS AT LAW

Wayne H. Matelski

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW Washington, DC 20036-5339
Phone 202/857-6000 Fax 202/857-6395 www.arentfox.com

Direct 202/857-6340
matelskw@arentfox.com

BY COURIER

COPY

December 8, 1998

Document Room 9B-23
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-170)
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-971 for Septanest® (Articaine Hydrochloride 4% with Epinephrine 1/100,000 and 1/200,000)
Sponsor Company: Deproco, Inc., 245-C Quigley Blvd., New Castle, Delaware 19720
RESPONSE TO RECOMMENDATION OF LABELING AND NOMENCLATURE COMMITTEE

Dear Madam/Sir:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its parent company, Spécialités Septodont, the manufacturer of Septanest® products, I am responding to Dr. Cynthia McCormick's letter dated November 24, 1998 (see attached) concerning NDA 20-971. In her letter, Dr. McCormick noted that the FDA's Labeling and Nomenclature Committee recommended that the Sponsor change the proposed name for Septanest® — (articaine hydrochloride 4% with epinephrine 1/100,000) by replacing the " — " with the epinephrine dosage strength. The Sponsor has considered this recommendation and proposes the following new names for its two products:

Product	Name Proposed in NDA 20-971 Submitted on March 30, 1998	New Name Proposed
Articaine hydrochloride 4% with Epinephrine 1/100,000	—	—
	—	—

If you have any questions or comments concerning the proposed names, please contact me.

Thank you for your assistance.

Very truly yours,

Wayne H. Matelski/BW

Wayne H. Matelski
U.S. Agent for and Counsel to
Spécialités Septodont and Deproco, Inc.

Attachments

Redacted 2

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DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD170/Nolan

Food and Drug Administration
Rockville MD 20857

NOV 24 1998

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialities Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (Articaine Hydrochloride 4% with Epinephrine 1/200,000 solution for injection) and Septanest — (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection) for infiltration and nerve block anesthesia in general dentistry.

We would like to share with you the recommendations of the Labeling and Nomenclature Committee regarding your proposed proprietary name.

In your submission you proposed Septanest — and Septanest — as the tradename for your product. The Labeling and Nomenclature Committee recommends that you use the epinephrine dosage strength instead of using — and highlight the concentration to denote difference in strengths. The use of — following the name is misleading as in the United States "SP" means "Spinal." The proposed tradename Septanest was determined to be acceptable.

If you have any questions, contact Ken Nolan, Project Manager, at 301-827-7410.

Sincerely,

/S/ MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III