CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

JAN 9 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

Per your November 21, 1997 request for all relevant reviews of the Actiq NDA, attached are reviews which were not apart of the FDA's Anesthetic and Life Support Drugs Advisory Committee meeting package material dated September 17, 1997.

The attached reviews are Statistical Review dated October 29, 1997; Pharmacology Reviews dated October 7, 1997, and March 17, 1997; Chemistry Reviews dated November 12, 1997, October 10, 1997, October 7, 1997, September 12, 1997, July 16, 1997, August 13, 1997, February 26, 1997; and Clinical Review dated October 10, 1997.

If you have any questions, please contact me at (301) 443-3741.

Sincerely,

/S/

Ken Nolan
Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-747
HFD-170/Div. files
HFD-103/Office Director
HFD-820/ONDC Office Director
HFD-820/ONDC Division Director
HFD-170/CMcCormick
HFD-170/RKahn
HFD-170/LLandow
HFD-170/KHaberny
HFD-170/DJean
HFD-170/PMaturu
HFD-170/AD'Sa
HFD-170/YTsong
HFD-170/TPermutt
HFD-170/MKlein
HFD-170/SDoddapaneni
HFD-170/DConner
HFD-170/CMoody
HFD-170/KNolan
HFD-44/SSherman
HFD-44/TAbrams
HFD-324/MThomas
HFD-021/KTempleton-Somers

Drafted by: KEN/m:/n20747.j12; n20747.s12; n20747.n12
Initialed by:
final:

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NLAN

Food and Drug Administration
Rockville MD 20857

NDA 20-747

AUG 26 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

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

We refer to the teleconference between representatives of your firm and FDA on July 23, 1998.

As requested, 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) 443-3741.

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 20-747
HFD-170/Div. files
HFD-170/CMcCormick
HFD-170/BRappaport
HFD-170/CCortinovis
HFD-170/KHaberny
HFD-170/DJean
HFD-170/PMaturu
HFD-170/AD'Sa
HFD-170/YTsong
HFD-170/TPermutt
HFD-170/MKlein
HFD-170/SDoddapaneni
HFD-170/JHunt
HFD-170/CMoody
HFD-170/KNolan
HFD-44/SSherman
HFD-44/TAbrams
HFD-324/MThomas
HFD-021/KTempleton-Somers

Drafted by: KEN/July 24\n:\cso\nolan\n20747mm.723
Initialed by:
final: 7-24-98

GENERAL CORRESPONDENCE (MINUTES SENT)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

JUL 31 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

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

We refer to the teleconference between representatives of your firm and FDA on June 26, 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) 443-3741.

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 20-747
HFD-170/Div. files
HFD-170/CMcCormick
HFD-170/BRappaport
HFD-170/CCortinovis
HFD-170/KHaberny
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HFD-170/PMaturu
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HFD-170/JHunt
HFD-170/CMoody
HFD-170/KNolan
HFD-44/SSherman
HFD-44/TAbrams
HFD-324/MThomas
HFD-021/KTempleton-Somers

Drafted by: KEN/July 12, 1998\n:\cso\nolan\n20747ml.626\Rev. July 13, 1998\\Rev. July 14, 1998
Initialed by:
final:

GENERAL CORRESPONDENCE (MINUTES SENT)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

APR 10 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

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

As requested, a copy of our minutes of that meeting is enclosed. Also attached is an extract from the September 17, 1997 ALSAC Meeting that the Agency commented on during the February 13, 1998 meeting.

If you have any questions, please contact Ken Nolan, Consumer Safety Officer at (301) 443-3741.

Sincerely,

/S/

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

Attachments

cc:
Original NDA 20-747
HFD-170/Div. files
GCF-001/LDickinson
HFD-170/CMcCormick
HFD-170/KHaberny
HFD-170/DJean
HFD-170/PMaturu
HFD-170/AD'Sa
HFD-170/YTsong
HFD-170/TPermutt
HFD-170/MKlein
HFD-170/SDoddapaneni
HFD-170/JHunt
HFD-170/DConner
HFD-170/CMoody
HFD-170/KNolan
HFD-44/SSherman
HFD-44/TAbrams
HFD-44/NOstrove
HFD-324/MThomas
HFD-021/KTempleton-Somers

Drafted by: KEN/m:/n20747ml.j30/February 23, 1998/Rev. Moody-ken/March 3, 1998//Rev. March 25, 1996
Initialed by:
final:

GENERAL CORRESPONDENCE (Minutes Sent)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

HFD 170/Nolan

NDA 20-747

NOV 4 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, and 1600 µg (fentanyl base).

We acknowledge receipt of your correspondence dated September 22, 1998, October 30, 1998, and November 4, 1998 in which agreed to the following Phase 4 commitments:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

MAR 30 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

We refer to the meeting between representatives of your firm and FDA on January 30, 1998 and February 13, 1998.

As discussed during these meetings attached is a very preliminary draft regarding Actiq's patient package insert. This draft is not conclusive and we recommend you address these concerns in the development of your product.

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

Sincerely,

/S/

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

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

MAR 4 1997

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your new drug application for Actiq™ (oral tansmucosal fentanyl citrate) 200μg, 400μg, 600μg, 800μg, 1200μg, and 1600μg.

In reviewing your request for trademark review, the Labeling and Nomenclature Committee has concluded the following:

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name. However, the Committee believes the established name for the product is (fentanyl citrate lozenge). The USP does not specifically recognize the term "oral transmucosal" and to be in conformance with the USP established name conventions, "oral transmucosal" should not be used. The Committee does recognize that "oral transmucosal fentanyl citrate" has been designated by the FDA for products in a similar class.

The Committee has no reason to find the proposed proprietary name unacceptable.

If you have any questions, please contact Millie Wright, Project Manager, at (301) 443-4250.

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

20-747
304-47

cc:
Original NDA 20-747
HFD-170/Div. Files
HFD-170/M.Wright
HFD-170/Maturu

Drafted by: M.Wright/February 27, 1997
Initialed by: CPMoody/3-3-97
final: sl/3-4-97

GENERAL CORRESPONDENCE

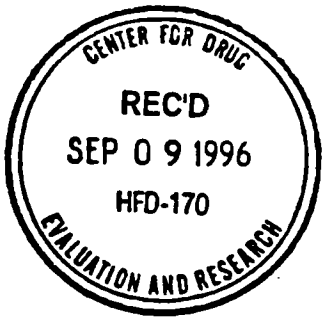
DUPLICATE

N(GC)304

ANESTA CORP.
4745 Wiley Post Way, Suite 650
Salt Lake City, UT 84116
801. 595.1405

Airborne Express

September 5, 1996



Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Attention: Document Control Room 9B23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: IND
Oral Transmucosal Fentanyl Citrate (OTFC) - Chronic Pain
Actiq™ - Request for Trademark Evaluation

Dear Sir/Madam:

Reference is made to the subject IND and to the clinical trial program involving the use of OTFC in the treatment of breakthrough pain in opioid-tolerant patients with cancer. The Phase 3 clinical trial program has been completed and Anesta Corp. intends to submit an interactive new drug application later this year. We wish to inform the reviewing division that a trade name, Actiq, has been selected for the drug product.

The purpose of this communication is to request a trademark evaluation by agency personnel (eg, reviewing division, Labeling and Nomenclature Committee). For your convenience, information concerning the drug product and its intended use is provided below.

Proprietary Name:	Actiq™
Established Name:	Oral Transmucosal Fentanyl Citrate
Proposed Indication:	Indicated for the management of chronic pain, particularly breakthrough pain, in patients already on and tolerant to opioid therapy.
Description:	A solid formulation of fentanyl citrate, a potent narcotic analgesic, intended for oral transmucosal administration. It consists of a lozenge on a paper stick and is consumed by sucking the dosage form. The inactive ingredients are sucrose, liquid glucose, artificial raspberry flavor, and white dispersion G.B. dye.
How Supplied:	Six doses of fentanyl citrate equivalent to 200, 400, 600, 800, 1200, or 1600 mcg of fentanyl base. Each dose may be identified by the text on both the outer wrapper and paper stick.

We are hopeful that the trademark will be acceptable to the agency. If you wish to discuss this request, please contact me by telephone (801.321.7456) or by facsimile (801.321.7490).

Sincerely,

Patricia J. Richards

Patricia J. Richards
Director, Regulatory Affairs

cc: Millie Wright, Project Manager (HFD-170)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATIONS (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21CFR 312.40).

1. NAME OF SPONSOR
Anesta Corp

2. DATE OF SUBMISSION
September 5, 1996

3. ADDRESS (*Number, Street, City, State and Zip Code*)
4745 Wiley Post Way, Suite 650
Salt Lake City, UT 84116

4. TELEPHONE NUMBER (*INCLUDE AREA CODE*)
(801) 595 1405

5. NAME(S) OF DRUG (*Include all available names: Trade, Generic, Chemical, Code*)
Fentanyl Citrate

6. IND NUMBER (*If previously assigned*)

7. INDICATION(S) (*Covered by this submission*)
For anesthetic premedication in children and adults, for use in anesthesia or monitored anesthesia care, and for treatment of chronic pain in opioid tolerant patients.

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ (*Specify*)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), DRUG MASTER FILES (*21 CFR 3114.420*), AND PRODUCT LICENSE APPLICATIONS (*21CFR Part 601*) REFERRED TO IN THIS APPLICATION.

NDA 20-195 Fentanyl Oralet® (Oral Transmucosal Fentanyl Citrate)
DMF
DMF
DMF
DMF

10. *IND submission should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission(e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 3 0 4

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (*Check all that apply*)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☒ OTHER Trademark Evaluation - Request (*Specify*)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
	CENTER FOR DRUG REC'D SEP 0 9 1996 HFD-170 EVALUATION AND RESEARCH	DIVISION ASSIGNMENT:

FORM FDA 1571 (5/95) PREVIOUS EDITION IS OBSOLETE

EF

12. **CONTENTS OF APPLICATION**

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

- ☒ 1. Form FDA 1571 *[21 CFR 312.23 (a)(1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a)(5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a)(6) (iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a)(6) (iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a)(6) (iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a)(7))(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS.

Michael A. Busch, Ph.D.
Vice President
Clinical Research & Regulatory Affairs

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Steven A. Shoemaker, M.D.
Vice President
Medical Affairs

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Patricia J. Richards Director, Regulatory Affairs	Patricia J. Richards	
18. ADDRESS *(Number, Street, City, State and Zip Code)* 4745 Wiley Post Way, Suite 650 Salt Lake City, UT 84116	19. TELEPHONE NUMBER *(Include Area Code)* (801) 595-1405	20. DATE September 5, 1996

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

WORKMAN
NYDEGGER
&SEELEY
ATTORNEYS AT LAW
A PROFESSIONAL CORPORATION
1000 EAGLE GATE TOWER
60 EAST SOUTH TEMPLE
SALT LAKE CITY, UTAH 84111
TELEPHONE (801) 533-9800
FACSIMILE (801) 328-1707

H. ROSS WORKMAN
RICK D. NYDEGGER
DAVID O. SEELEY
BRENT P. LORIMER
THOMAS R. VUKSINICK
LARRY R. LAYCOCK
JONATHAN W. RICHARDS
DAVID R. WRIGHT
JOHN C. STRINGHAM
MICHAEL F. KRIEGER
BRADLEY K. DESANDRO
JOHN M. GUYNN
GREGORY M. TAYLOR
DANA L. TANGREN
KEVIN B. LAURENCE
ERIC L. MASCHOFF

SUSAN K. THOMAS
JEFFREY L. RANCK
CHARLES J. VEVERKA
JONATHAN D. WOOD
ROBYN L. PHILLIPS
DAVID B. DELLENBACH
TIMOTHY M. FARRELL
JOHN N. GREAVES
VANESSA B. PIERCE
LENA I. VINITSKAYA
KEVIN K. JOHANSON

PATENT
TRADEMARK
COPYRIGHT
TRADE SECRETS
UNFAIR COMPETITION
LICENSING
COMPLEX LITIGATION

INTERNET
HOME PAGE: http://www.wnspat.com
GENERAL E-MAIL: info@wnspat.com

October 3, 1997

VIA HAND DELIVERY

Ms. Patricia Richards
Director of Regulatory Affairs
ANESTA CORPORATION
4745 Wiley Post Way
Plaza 6, Suite 650
Salt Lake City, Utah 84116

RE: Certification Letter
Our File No.: 10304.1

Dear Ms. Richards:

This letter will serve to certify that U. S. Patent No. 4,671,953 issuing to Theodore H. Stanley and Brian Hague, entitled "METHODS AND COMPOSITIONS FOR NONINVASIVE ADMINISTRATION OF SEDATIVES, ANALGESICS, AND ANESTHETICS" contains method of use and composition claims. This patent has composition claims directed to the pending Actiq™ and product designated (NDA 20-747).

Cordially,

WORKMAN, NYDEGGER & SEELEY

Michael F. Krieger

MFK:mlm
Enclosure

G:\DATA\WPDOCS2\MLM\MFK\1003LTR.RIC

ANESTA

ANESTA CORP

4745 Wiley Post Way Suite 650
Salt Lake City, Utah 84116

September 25, 1998

Cynthia McCormick, M.D.
Director
Division of Anesthetics, Critical Care, and
Addiction Drug Products (HFD-170)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane (Room 9B-45)
Rockville, Maryland 20857

Re: Approval of Actiq® Under Subpart H

Dear Dr. McCormick:

Anesta Corp., Abbott Laboratories, and the Division have had extensive discussions about how to assure the safe use of *Actiq*. Anesta believes that the Risk Management Program, as submitted, provides adequate assurance. Center and Division officials believe that, in addition, *Actiq* should be approved pursuant to Subpart H of the NDA review regulations, 21 C.F.R. §§ 314.500-.560, to allow for expedited withdrawal under § 314.530, should there be a safety problem, and to provide for advance review of promotional materials under § 314.550. It is Anesta's understanding that restrictions on distribution or use under § 314.520 would not be required as part of a Subpart H approval.

Anesta Corp. is willing to accept Subpart H approval of *Actiq* on those terms. We continue to have serious questions about the applicability of Subpart H to *Actiq*. Nevertheless, the provisions of Subpart H that the Center and Division believe are important are consistent with Anesta's objective of obtaining authorization to market *Actiq* for use by cancer patients suffering breakthrough pain. Consequently Anesta agrees to approval of *Actiq* under Subpart H on the terms that the Center and Division have proposed, as set forth in this letter.

There are two matters of implementation we wish to raise in this letter. We recognize that there may be others that are unforeseen.

First, § 314.550 contemplates that all issues regarding promotional material will not only be raised but also resolved within the 30-day advance review period. Anesta and the Center must both be prepared to act expeditiously concerning any issues relating to *Actiq* promotional material.[1]

1/ As to the submission of promotional material to be used within 120 days of approval, we are awaiting feedback on proposed labeling so that these draft materials can be prepared. These materials will not be finalized for use until the Agency has completed its consideration. We look forward to working out a mutually satisfactory timetable for this process.

p. 801 595 1405
f. 801 595 1406

Second, § 314.530 provides for expedited withdrawal of approval on six specified grounds pursuant to Part 15 hearing procedures. Anesta requests that, if the Center considers withdrawing *Actiq*'s approval because of safety concerns, and Anesta believes there is a question about the scientific basis for those concerns, the Center consider consulting the appropriate standing advisory committee before commencing a Subpart H withdrawal proceeding. Of course, Subpart H (including the advisory committee under § 314.530(e)) would still be available if the Center and Anesta continued to disagree.

These two implementation items are not conditions for Anesta's acceptance of Subpart H. They are, as stated, matters of implementation to be addressed after approval and on the basis of the circumstances existing at the time.

Based on recent communications, Anesta understands that the Center and Division intend to issue an approval letter, rather than an approvable letter, as final action under the agency's User Fee Act commitments. Anesta intends to support this objective by responding fully to the remaining items identified during the August 26 meeting. With those responses, and Anesta's acceptance of approval under Subpart H, issuance of an approval letter on or before October 30 will be feasible. It is important to Anesta that this action consist of an approval letter. If our understanding as to your current intention in this respect is in error, we would appreciate your so advising us upon receipt of this letter.

Anesta believes that marketing experience will demonstrate that *Actiq* is safe under the Risk Management Program. Anesta will ask the Division to reconsider the necessity for Subpart H oversight pursuant to § 314.560 at an appropriate time.

Anesta appreciates the time and attention that you, Dr. Lumpkin, and other FDA staff have devoted to the *Actiq* NDA. We reiterate Anesta Corp. and Abbott Laboratories' commitment to the safe use of *Actiq* and to the rigorous execution of the Risk Management Program. We will continue to work with you to complete the Division's action on the NDA and, thereafter, to continue a constructive dialogue with the Division on *Actiq* and to expeditiously resolve issues as they arise in consultation with the Division. If you have questions, please contact me.

Sincerely,

for Thomas B. King

Thomas B. King
President and CEO

cc: Murray M. Lumpkin, MD, Deputy Director for Review Management, HFD-002
Ken Nolan, Project Manager, HFD-170
Tom Willer, PhD, Abbott Laboratories

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

APR 10 1998

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

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

As requested, a copy of our minutes of that meeting is enclosed. Also attached is an extract from the September 17, 1997 ALSAC Meeting that the Agency commented on during the February 13, 1998 meeting.

If you have any questions, please contact Ken Nolan, Consumer Safety Officer at (301) 443-3741.

Sincerely,

/S/

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

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-747

Anesta Corporation
4745 Wiley Post Way, Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

NOV 13 1997

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated November 11, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq ™ (oral transmucosal fentanyl citrate, OTFC) 200, 400, 600, 800, 1200, & 1600 μg (fentanyl base).

We acknowledge receipt of your submissions listed in Attachment 1. The User Fee goal date for this application is November 13, 1997.

Since the September 17, 1997 Anesthetic and Life Support Advisory Committee meeting, the Division has conducted a more detailed review of this application. We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Issues Relating to Clinical Efficacy and Safety

1. The single pivotal study in support of the indication of chronic pain, particularly breakthrough cancer pain in patients on chronic opioids, Study AC200/013, has been reviewed and several clinical study sites investigated. It appears that the study may not have been blinded and also that OTFC from the titration phase may have been used instead of placebo. The extent of these problems is not clear at this time. These findings make the placebo response against which the clinical effect of the drug was measured unreliable.

2. There has not been an accurate accounting of dosing during the clinical studies in patients with cancer pain. This includes adequate accounting for completion of units during the clinical studies and assessment of actual dose of Actiq ™ taken per episode. The lack of accounting of actual doses rendered the evaluation of adverse events as a function of dose, inaccurate and incomplete. In addition, a careful analysis of the safety of each of the proposed doses in the population intended for this product and

also as a function of the dose of background medication was not performed. The analysis should have included adverse events, serious adverse events, withdrawal due to adverse events and deaths which occurred in patients still taking the medication. Consequently at this point labeling cannot be written to describe adequately the risks of this product at various doses in the intended population. This needs to be further discussed.

The titration scheme submitted on September 26, 1997 which is proposed for the introduction of this product in a range of doses from 200 to 1600 μg was not prospectively studied. A prospective safety evaluation of such a titration scheme is necessary.

3. The risks of unintended overdose in opiate-tolerant and opiate-naive patients or accidental ingestion associated with this product if used at home are significant. We draw your attention to the Risk Management Plan submitted as part of the NDA. We consider the quality, content, and proper implementation of such a plan essential to the safe introduction of this product to the market. The current plan is incomplete and not commensurate with the risk inherent in marketing this product for use at home. The plan at its core should address an unambiguous design of the unit, analysis of appropriate doses for marketing, child protective packaging tested in children >4 years of age as well as in the younger ages, provisions for informed consent, safety measures to secure the product prior to and after its use, improved warnings to protect against unintended overdose or accidental ingestion, guidelines and educational programs for use or overdose, education of health professionals, labeling of the product to limit unsafe prescribing, focused marketing, limitations on number of units at home, surveillance and reporting mechanisms.

Issues Relating to Chemistry and Manufacturing

1. The handle change based on the Abbott drawing submitted on September 22, 1997 lacks supporting stability data and process validation on production size batches with the modified handle.

2. The handle design based on the Abbott drawing submitted on September 22, 1997 also is deficient from the standpoint of safety. Because this potent medication looks like a candy, it is very important that adequate information and multiple cues be included in the design of the product handle.

In addition, we have the following comments:

> Studies AC200/011 and AC200/012 have demonstrated that a "successful" dose could be found based on both pain relief and tolerability. However, the steps needed to establish efficacy in that dose in a controlled manner were not performed in these titration studies. These studies do not provide adequate evidence for efficacy, as we have indicated in the past.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed.

We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

We encourage you to continue exploring further development of OTFC regarding pain in cancer patients and welcome the opportunity to meet with you to discuss the specific requirements in refining this product.

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

Sincerely yours,

/S/

Cynthia 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

Enclosure: Attachment 1-Amendment Dates