CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-747 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170 Trade (generic) name/dosage form: Actiq (OTFC) oral transmucosal fentanyl citrate Action: AP

Applicant Anesta Therapeutic Class 3S

Indication(s) previously approved _____ Pediatric labeling of approved indication(s) is adequate _____ inadequate _____

Indication in this application only for the management of breakthrough cancer pain in patients with malignancies who are tolerant to opioid therapy for their underlying persistent cancer pain. (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

X b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

X (4) If no protocol has been submitted, explain the status of discussions on the back of this form. **(Please see attached Phase IV Commitment for Studies in Pediatric Patients.)**

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. PEDIATRIC STUDIES ARE NOT **NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

Signature of Preparer and Title (PM, 050, MO, other)

11/4/98

Date

cc: Orig NDA#20-747
HFD-170/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

signed CGm 11/10/98

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

2. (b) 4 Pediatric Studies Are Needed

STUDIES IN PEDIATRIC PATIENTS

A program to study appropriate dosing paradigms and safety profile in opiate tolerant pediatric cancer patients with breakthrough pain which will lead to informed prescribing instructions in the label—addressing appropriate starting dose, titration schedule, and safety at labeled doses—will be conducted. Patients will be dosed in a manner similar to the conditions defined in the Actiq prescribing information (modified as needed based on PK and tolerance). Safety under these conditions will be assessed with modifications based on pharmacokinetics and tolerance. The program will be designed to obtain specific safety information in the dosage range studied in pediatric patients. A secondary analysis of additional risk to families with other children in the home and a plan for managing that risk including an evaluation of the role of antagonist therapy will be submitted. Concurrence will be reached with FDA on the final design of this program. This program will be completed within the first two years after approval.

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

December 20, 1996

45 Day Meeting for NDA 20-747: Oral Transmucosal Fentanyl as ACTIQ

Medical Officer's Summary
Roberta C. Kahn, M.D.

Oral transmucosal fentanyl is a solid formulation of fentanyl citrate incorporated into a sweetened soluble matrix on a handle, intended for oral administration by sucking. By this route, fentanyl has a bioavailability of approximately 50%, representing a combination of rapid absorption through the transmucosal route and slower absorption through swallowing and absorption through the gastrointestinal tract.

The sponsor is currently marketing this product as Fentanyl Oralet 100, 200, 300 and 400 μg (NDA 20-195) for use as a pre-anesthetic sedative and as an analgesic/sedative for painful invasive procedures. At the time of approval of Fentanyl Oralet, it was the intention of the sponsor to conduct further studies to support an indication in chronic treatment of patients with cancer pain. It is this indication which is the subject of the current NDA.

The Proposed Labeling

The product will be prepared in six strengths equivalent to 200, 400, 600, 800, 1200, and 1600 μg fentanyl base. The different strengths are written on the outer wrappers and product handles, which are different colors for each strength.

As per prior discussions with this division the product is renamed Actiq and the candy matrix is off-white in color. The lemon flavor originally proposed for this application was discontinued because of manufacturing problems. Consequently, the formulation of Actiq contains raspberry flavor as in the original formulation of Fentanyl Oralet.

Following are **statements from the proposed labeling,** with *comments by this reviewer.* References to the approved labeling for Fentanyl Oralet, or to the supportive studies of this NDA are identified whenever possible.

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

List of Controlled Clinical Studies:

1. **AC 200/013** A Multicenter, Double-Blind, Placebo Controlled Crossover Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Opioids.

2. **AC 200/006** Multicenter Study of the Analgesic Effect of OTFC and Morphine PCA in Patients Undergoing Joint Arthroplasty.

3. **AC 200/001** Compassionate Use of OTFC in Patients for Postoperative Pain.

4. **AC 200/011** A Dose Titration, Multicenter Study of OTFC for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Oral Morphine.

5. **AC 200/012** A Dose Titration, Multicenter Study of OTFC for the Treatment of Breakthrough Pain in Cancer Patients Using Transdermal Fentanyl.

6. **AC 200/010** A Double-Blind Randomized Four-Point, Parallel Group, Multicenter Study of the Potency of Two Doses of OTFC Relative to Intravenous Morphine for the Treatment of Acute Postoperative Pain in Patients Recovering from Lower Abdominal Surgery.

7. **AC 200/P10** A Double-Blind, Randomized, Parallel Group Pilot Study of Two Doses of OTFC for the Treatment of Postoperative Pain in Patients Recovering from Lower Abdominal Surgery.

NDA 20-747
Final Minutes of Meeting
June 12, 1997

Abbott Laboratories Attendees:
Robert DeNoto, Manager Advanced Drug Delivery
Steven Good, Packaging Engineer
John Heden, Business Director, Pain Management
James Raihle, Director, Program Management
Thomas Willer, Ph.D., Assistant Director, Regulatory Affairs

Anesta Corporation Attendees:
Thomas B. King, President and COO
Earl Nordbrock, Ph.D., Director, Statistics and Clinical Data Management
Patricia J. Richards, Director, Regulatory Affairs

FDA Attendees:

Curtis Wright, M.D., M.P.H.
Acting Division Director, HFD-170

Eric Sheinin, Ph.D.
ONDC, Director

Abi D'Sa, Ph.D.
Team Leader, Chemistry

John Gibbs, Ph.D.
DNCD II, Director

Pat Maturu, Ph.D., M.B.A.
Chemist

Corinne Moody
Chief, Project Manager, HFD-170

Ken Nolan
Project Manager

Discussion Topics

1. Introduction of FDA and Anesta attendees.

2. The Agency stated the purpose of the meeting is to understand chemistry issues and attempt to resolve these issues by November 1997. Requested questions regarding other disciplines are deferred until a later date.

3. Anesta's presentation included:
   a. • Display of preferred Actiq and Oralet products and noted the differences between the products
      • Bracketing Design protocol

- Stability of Actiq
  - 12 lots 3 each at 200, 600, 1600; 1 each at 400, 800, 1200; 25ºC/60% relative humidity
  - 6 lots at 40ºC/75% relative humidity
  - 6 lots at 40ºC/75% less than 20% relative humidity

Please note: The term "preferred Actiq" refers to the design of Actiq drug product in comparison to the NDA 20-195 Anesta's Oralet design.

b. Discussed concerns regarding low humidity (i.e., absolute vapor). Reportedly, Anesta does not have an approved chamber. Therefore, data not included in application.

4. Full production batches including discussion regarding intermediate points (i.e., 3, 6, 9, 18, and 24 months). Reportedly, accelerated data will be available at 6 months.

5. Discussed Actiq Pouch and child resistance including the use of "valeron" which is used to in the design of the pouch to inhibit access.

6. Reportedly, there is not any stability data available regarding melting, moving, and deformation of the product. Anesta proposes to supply data.

7. Anesta conveyed that by August 1997, 11 months (i.e., from September 1996 to August 1997) of stability data will be available. Also, 9 months of test data will be available in August 1997.

8. Discussed design of product including 1) the shape of stick (i.e., the product is designed similar to a lollipop); 2) the small print on the product; 3) the facility and machinery used in the design product. Anesta reports, the drug matrix, stick and the pouch are stable and that. Low humidity levels were used to meet DEA requirements.

9. Agency's Clinical Concerns included:

- Labeling on stick is small
- Unit separates from an outer package
- Pouch conformity to Poison Prevention Act recommendations
- Request for child resistance test data.

10. Agency's Chemistry Concerns included:

a. <u>Stability</u>
- Recommendation for adherence to ICH's Guidelines for 12 months of stability data at time of application submission. It was noted that this application only has 1 month of

stability data for 3 strengths.
- Expiration dates will be shortened due to stability data submitted in application.
- Data for 3 batches needed at 25ºC.
- The statistician will review applicable data.

b. **Bracketing**
- Clarification that bracketing is done when formation is the same; different inactive and active.
- Clarification that batches with the least data will determine expiration dates.

11. Anesta presented tabular information comparing Actiq with proposed fentanyl dosages, and rationale of active versus inactive ingredients.

12. Discussed primary stability data for Oralet and whether this could be supportive data, since Oralet has a different pouch design than Actiq.

- Mutually agreed that Oralet has 24 months of stability data and rate limiting batches has 6 months of data.

13. Clarified ICH guidelines are guidance and cannot be enforced. If a different approach is taken, the applicant will have to prove on a case-by-case situation. Additional clarification given regarding stability data in reference to expiration dates:
    a. 12 months at 25ºC will yield 1 year expiration date.
    b. 6 months of accelerated stability data is acceptable at the Division's discretion, however expiration dates are usually set by taking the actual data and adding 6 months.

14. The Agency conveyed it will request an Advisory Committee Meeting to discuss safety issues regarding Actiq.

15. The Agency conveyed that an internal labeling meeting will be held and comments will be forwarded to the applicant with the action letter. Therefore, the Agency will not host an NDA Day (i.e., meet with the sponsor to discuss labeling concerns).

16. The Agency recommended the following options to Anesta regarding chemistry concerns and the effects it may have on the entire application:

Option 1: Launch with NDA 20-195's package configuration for NDA 20-747.

Option 2: Launch with the preferred Actiq packaging with a short expiration date. Expiration dating could be extended based on acceptable stability results from the full 12 production batches currently on stability. Obtain pre-clearance from chemist to submit data in annual reports.

Option 3: Receive an approvable regulatory action, then launch with the preferred Actiq packaging, pending the acceptability of data as it becomes available. This will also protect exclusivity rights.

17. Reviewed bracketing and matrixing data. Anesta agree to submit 6 months update on first 3 lots of stability, and 6 months data on 2nd 3 lots by July 1997.

18. Discussions on Oralet concerns were deferred. However, it was noted that Oralet was a supplemental application and 3 lots per strength were submitted. Also, it was noted that due to very little data being submitted resulted in short expiration dates.

19. Anesta presented Rationale for Design slides.

20. Clarified that ICH Guidelines agreement may be applicable if the proposed Brussels Meeting is held.

21. The Agency restated:

Option 1: Launch with NDA 20-195's package configuration for NDA 20-747.

Option 2: Launch with the preferred Actiq packaging with a short expiration date. Expiration dating could be extended based on acceptable stability results from the full 12 production batches currently on stability. Obtain pre-clearance from chemist to submit data in annual reports.

Option 3: Receive an approvable regulatory action, then launch with the preferred Actiq packaging, pending the acceptability of data as it becomes available. This will also protect exclusivity rights.

22. Reiteration of Agency's request for Anesta to submit stability data to NDA 20-747.

23. Anesta proposed to update stability reports and submit accordingly.

24. Anesta stated that the change in stick design from Oralet packaging design was due to manufacturing design and cost.

25. The Agency addressed potential Advisory Committee concerns including:
- dosages of fentanyl in a drug product that could be mistaken as a food product
- child resistance packaging
- differences between Oralet and preferred Actiq including strength identification and handle design.

26. The Agency proposed labeling comments will be forwarded by August 1997.

27. Discussed that the pre-approval inspection has been made and Environmental Assessment deficiencies were noted. Anesta reports they have not been contacted by the District Office regarding chemistry concerns.

28. DSI Investigations at 4 of the 6 sites were noted as Voluntary Action Indicated (VAI).

29. Anesta will submit:
    - Child resistance data
    - Absolute vapor documentation
    - to annual report data on extension of shelf-life
    - update on stability data.

30. The Agency requested Anesta to submit a cost analysis should modification of the product (i.e., redesign of stick) be pursued. These modifications are noted in items 8, 9, and 25.

31. As an alternative to receiving a not approvable action in November 1997 the 3 options listed items 16 and 21 were restated.

Minutes Preparer:

DEC 20 1996

Memorandum of 45 Day Filing Meeting

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

Date: December 20, 1996 Time: 10AM

NDA: 20-747 Sponsor: Anesta Corp.

Tradename: Actiq™ (oral transmucosal fentanyl citrate, 200μg, 400μg, 600μg, 800μg, 1200μg, and 1600μg.

Indication: Management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy.

Date NDA Submitted: November 11, 1996

Date Received: November 13, 1996

On December 20, 1996 an in-house meeting was held in 9B-45 by the team members reviewing NDA 20-747. In attendance were the following:

Roberta Kahn, Medical Officer
Larry Landow, Medical Officer Team Leader
Pat Maturu, Chemist
Tom Permutt,BioStat Team Leader
Yi Tsong, Statistician
Kathy Haberny, Pharmacologist
Suresh Doddapaneni, Pharmacokineticist
Mike Klein, Drug Abuse Reviewer
Mark Atkins, DDMAC
Charles Snipes, DSI/Pre-Clinical
Indira Kumar, Project Manager
Millie Wright, Project Manager

The reviewers from each discipline briefly verified that this NDA 20-747 is sufficiently complete to file under 21 CFR 314.101(a). Therefore, the NDA is considered filed on January 10, 1997 (The 60 day deadline was on January 12, which was Sunday.)

/S/ 1/10/97

Millie Wright, Project Manager

45 Day Filing Meeting for NDA 20-747(cont)

CC:
Orig NDA 20-747
HFD-170/Div File
HFD-170/M.Wright;Kumar; Kahn; Landow; D'Sa; Maturur; Permutt;
Tsong; Jean; Haberny; Doddapaneni; Klein; Moody;

Attachments ~~(6)~~ (7)

~~JUL 28~~

MEMORANDUM OF TELECONFERENCE MINUTES

JUN 26

Meeting Date: June 26, 1998
Time: 5:00 p.m.
Location: 9B-45

Application: NDA 20-747 (Anesta) Actiq

Type of Meeting: Guidance Meeting

Meeting Chair: Cynthia McCormick, M.D., Division Director

Meeting Recorder: Ken Nolan, Project Manager

Objective: The Agency's objective for this teleconference was to provide the sponsor a status update for the pending April 30, 1998 amendment to NDA 20-747.

Anesta Attendees:

Paul Litka, M.D., Vice President, Clinical Drug Development
Martha Arnold, MBA, Vice President, OTFC® Business Unit
John Marriott, Ph.D., Director Clinical Research, Marketed Products
Earl Nordbrock, Ph.D., Director, Statistics and Clinical Data Management
Karen Jones, Regulatory Affairs Associate

FDA Attendees:

Cynthia McCormick, M.D., Division Director
Bob Rappaport, M.D., Deputy Division Director
Albinus D'Sa, Ph.D., Team Leader, Chemistry
Corinne Moody, Chief, Project Management Staff
Ken Nolan, Project Manager

Discussion Topics

- Introductions and Opening Remarks
  - The Agency noted new members of the review team will be reviewing the April 30, 1998 submission.
  - The Agency stated its commitment to moving forward and keeping the lines of communication open

- Summary of Clinical Concerns:
  - The Agency noted in its preliminary review of the information included in the April

30, 1998 amendment that issues concerning blinding and efficacy may have been resolved.

- A follow-up teleconference to discuss questions concerning the safety analysis may be warranted pending the medical reviewer's assessment of the information.

- Summary of Chemistry, Manufacturing, and Controls Concerns:
  - Anesta asked if there were any chemistry issues.
  - In response, the Agency referenced and reiterated its comments as stated in Anesta's version of the February 13, 1998 meeting minutes (i.e., The Agency's comments were):
    > The expiry dating on the straight handle will be limited by stability testing submitted together with the commitments for stability on the first production batches.
    > With a significant redesign of the handle the Chemistry Review Team stated they would be willing to assist Anesta in reaching an acceptable solution to the product.
    > Final decisions would rest with the Office of New Drug Chemistry.

- Summary of Risk Management Program (RMP) Concerns:
  - The Agency stated its concerns regarding the RMP's limitations in addressing potential risks related to either accidental pediatric ingestion or use by opioid-naive patients.
  - The Agency will be prepared to share its specific concerns regarding the RMP during the proposed July 30, 1998 meeting.
  - To minimize risks associated with this product in the home, the Agency is seriously considering requiring a staged roll-out to affirm that enough data is collected pertaining to risks associated with Actiq.
  - The Agency suggested that Anesta provide a strategy for the staged roll-out.
  - Anesta requested the most recent physician labeling comments. In response, the Agency stated its willingness to share comments regarding the physician labeling and patient registry concerns that resulted from the Agency's review of the November 1996 submission. The Agency stated:
    > Recommendations for the physician labeling will be sent immediately.
    > Recommendations for the patient registry template will be sent at a later date (i.e., once the Division has refined the template that will be used for Anesta to model its patient registry).

Minutes Prepared: _____ Chair Concurrence: _____

cc: Original NDA 20-747
HFD-170/Div. Files
HFD-170/CMcCormick
HFD-170Bob Rappaport
HFD-170/AD'Sa
HFD-170CMoody

Drafted by:KEN\July 13, 1998\n:\cso\nolan\n20747mm.626
Initialed by:
final:

MEETING MINUTES

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Date: October 15, 1998

Application: NDA 20-747 (Anesta) Actiq

Type of Meeting: Guidance Meeting

Meeting Chair: Cynthia McCormick, M.D., Division Director

Meeting Recorder: Ken Nolan, Project Manager

Objective: The Agency requested this teleconference to verify incidences of somnolence noted in the patient insert submitted in the September 22, 1998 submission for NDA 20-747 (Anesta) Actiq.

Anesta Attendees:

Paul Litka, M.D., Vice President, Clinical Drug Development
Earl Nordbrock, Ph.D., Director, Statistics and Clinical Data Management
Patricia Richards, Director, Regulatory Affairs

FDA Attendees:

Bob Rappaport, M.D., Deputy Division Director
Charles R. Cortinovis, M.D., M.P.H., Medical Reviewer
Thomas Permutt, Ph.D., Statistics-Team Leader
Ken Nolan, Project Manager

Discussion Topics

The Agency requested this teleconference to verify incidences of somnolence noted in the patient insert submitted in the September 22, 1998 submission (i.e., raw data versus data submitted in the original NDA submission).

At the Agency's requests, Anesta agreed to submit data on individual patients with somnolence due to the Agency's difficulty computing its analysis of somnolence submitted in the patient insert.

Anesta will submit SAS data sets by Monday, October 19, 1998 containing the following parameters:

1. How each patient (n=50) was classified as to dose in the original ISS.
2. How each patient is classified as to dose in the two tables (titration and long-term) in the proposed labeling.

3. The dose for each episode of breakthrough pain, so that these classifications can be verified.

The Agency and Anesta expressed their gratitude for the teleconference, then the teleconference was terminated.

Minutes Prepared: _____ Chair Concurrence:

cc: Original NDA 20-747
HFD-170/Div. Files
HFD-170/CMcCormick
HFD-170Bob Rappaport
HFD-170/Cortinovis
HFD-170CMoody

Drafted by:KEN\October 16, 1998\n:\cso\nolan\n20747mm.O15
Initialed by:
final:

MEETING MINUTES

693

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: Division of Anesthetic, Critical Care and Addiction Drug	HFD-170
Attention: Millie Wright, Project Manager	Products Phone:443-4250
Date: 10/12/96	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Actiq	IND # NDA ~~XXXXX~~ #coming in 11/96 (Nov/96)
Established name, including dosage form: Oral Transmucosal Fentanyl Citrate	
Other trademarks by the same firm for companion products: Fentanyl Oralet NDA 20-195)	
Indications for Use (may be a summary if proposed statement is lengthy): Indicated for the management of chronic pain, particularly breakthrough pain, in patients already on and tolerant to opioid therapy	
Initial Comments from the submitter (concerns, observations, etc.): None. (For more information, see attached from Sponsor.)	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible. {Rev. August 95}

Consult #693 (HFD-170)

ACTIQ oral transmucosal fentanyl citrate

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.

/S/ 11/18/96, Chair
CDER Labeling and Nomenclature Committee

13. Patent Information

The following patent information is submitted in accordance with 21 CFR §314.53(c). Please note that it is the only patent relevant to this New Drug Application for Actiq™ (oral transmucosal fentanyl citrate). Patent No. 5,288,497 is not applicable to this application. The package insert will be revised accordingly.

A. Patent Information

Patent Number:	4,671,953
Expires:	May 1, 2005
Title:	Methods and Compositions for Noninvasive Administration of Sedatives, Analgesics, and Anesthetics
Type:	Composition; Method of Use
Issued To:	Theodore H. Stanley and Brian Hague
Agent:	Workman, Nydegger & Seeley Attorneys at Law 1000 Eagle Gate Tower 60 East South Temple Salt Lake City, UT 84111

B. Declaration

The undersigned declares that Patent Number 4,671,953 covers the composition or method of use of *Actiq*. This product is the subject of this application for which approval is being sought.

Signature: Patricia J Richards

Name: Patricia J. Richards

Title: Director, Regulatory Affairs, Anesta Corp.

Date: 30 October 1997

C. Statement of Exclusivity

The product *Actiq* is entitled to marketing exclusivity under Section 505(b) of the Federal Food, Drug, and Cosmetic Act and as provided in 21 CFR §314.108 (b)(4).

14. Patent Certification

Included in this section is a copy of an October 3, 1997, letter from Michael Krieger, Workman, Nydegger & Seeley (agent of the patent owner).

EXCLUSIVITY SUMMARY FOR NDA # 20-747 SUPPL #000

Trade Name Actiq Generic Name Actiq (oral transmucosal fentanyl citrate)

Applicant Name **Anesta Corporation** HFD # **170**

PDUFA Date November 4, 1998 Approval Date if known November 4, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES/_X__/NO /___/

b) Is it an effectiveness supplement?

YES /__/ NO / X _/

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

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

YES /_X__/ NO /___/

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

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

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

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

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

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-

covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

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

NDA# **20-195** **Oralet** (oral transmucosal fentanyl citrate)

2. Combination product.

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

YES /___/ NO /___/ N.A.

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

YES /___/ NO /_X__/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /_X__/

If yes, explain:

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

Investigation #1 Study # AC200/011

Investigation #2 Study # AC200/012

Investigation #3 Study # AC200/013

Investigation #4 Study # AC200/014

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/
Investigation #4	YES /___/	NO /_X__/

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

_____ _____

_____ _____

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

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X_/
Investigation #4	YES /___/	NO /_X__/

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

_____ _____

_____ _____

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

Investigation #1 Study # AC200/011

Investigation #2 Study # AC200/012

Investigation #3 Study # AC200/013

Investigation #4 Study # AC200/014

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

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

Investigation #1 Study # AC200/011

Investigation #2 Study # AC200/012

Investigation #3 Study # AC200/013

Investigation #4 Study # AC200/014

IND Yes /_X_/ No/___/ Explain:

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

Not applicable to this application.

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

YES /___/ NO /X/

If yes, explain: _____

_____

Signature: /S/
Title: Project Manager
Date: 11/4/98

Signature of Division Director /S/
Date: 11/5/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

15. Other

Debarment Statement

(1) Certification About the Use of a Debarred Person

It is certified "... that Anesta Corp. 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 (NDA 20-747)." [Section 306(k)(1) of the Generic Drug Enforcement Act (21 U.S.C. 335a(k)(1).]

(2) List of Relevant Convictions for Persons Debarred or Not Debarred

Anesta Corp. has no convictions to list for which any person can be debarred as described in Section 306(a) and (b) of the Generic Drug Enforcement Act.