NDA 20-747

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) 200, 400, 600, 800, 1200, and 1600 µg (fentanyl base).

We acknowledge receipt of your submissions dated April 30, July 29, September 4 and 22, October 9, 19, 29 and 30, and November 4, 1998. Your submission of April 30, 1998 constituted a complete response to our November 13, 1997 action letter. The user fee goal date is November 4, 1998.

This new drug application provides for the use of Actiq for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

We have reviewed this application under the restricted distribution regulations contained in 21 CFR 314.520 (Subpart H) and have concluded that restrictions on distribution and use of Actiq are needed to assure safe use of the product.

We have completed the review of this application, including the Actiq Risk Management Program (RMP) as amended. We have concluded that adequate information has now been presented to demonstrate that Actiq is safe and effective, when marketed in accordance with the terms of restricted distribution and use described in the Risk Management Program (attached to this letter), and as recommended in the attached final labeling text to which you agreed on November 4, 1998 in a telephone conversation between representatives of Anesta and of FDA.

Accordingly, under the provisions of 21 CFR 314.520, this application is approved effective on the date of this letter.

CHANGES TO THE ACTIQ RISK MANAGEMENT PROGRAM:

Please note that the attached Risk Management Program (RMP) is an integral part of the approved NDA for this product and is an essential component of the terms of this NDA's approval by FDA for marketing this product in the United States. As such, any proposed change(s) in the Risk Management Program must be submitted to FDA as a supplement to the NDA and any proposed change must have FDA prior approval before implementation. Changing the Risk Management Program without prior FDA approval may render the product misbranded and an unapproved new drug.

FUTURE INSPECTIONS:

In order to monitor the success of compliance with the restricted distribution provisions of this approval action, we intend to conduct inspections of Anesta Corporation's and Abbott Laboratories' records during the first or second quarter after launch. We will meet with you to discuss the inspections within one month after completion of the inspections. Inspections and meetings with you will continue periodically thereafter as appropriate.

SPECIAL ADVERSE EVENT REPORTING REQUIREMENT of the RISK MANAGEMENT PROGRAM:

Please note that, until further notice, you are required to report the following types of adverse events to the FDA within 15 calendar days (as "15 Day Alert Reports") of your receipt of the report:

- Any unintended pediatric exposure (<16 years of age), whether or not there is a serious outcome and whether or not the outcome was unexpected

- Any serious adverse drug experience which is determined to occur in the context of diversion (i.e., use by an individual other than for whom it was prescribed), whether or not the experience is unexpected

- Any serious adverse drug experience that is determined to occur in the context of "off

label use" (i.e., that is used outside of the approved indication for Actiq), whether or not the experience is unexpected.

Definitions of the above terms are as stated in 21 CFR 314.80. These special safety reporting requirements are in addition to the routine requirements for reporting of post-marketing adverse experience data established in 21 CFR 314.80.

FINAL PRINTED LABELING (including Professional Package Insert and Patient Package Insert):

The final printed labeling (FPL) must be identical to the attached approved final labeling text, including boxes, bolding, bullets, and other formatting provisions. Marketing the product with FPL that is not identical to this approved text may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available, in no case more than thirty days after it is printed. Please individually mount ten copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-747. Approval of this submission by FDA is not required before the labeling is used.

PHASE FOUR COMMITMENTS:

Please be reminded of your Phase 4 commitments, specified in your submission dated November 4, 1998. These commitments, along with any completion dates agreed upon are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

PROMOTIONAL ACTIVITIES:

Please note that promotional activities for this approved NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials that you

propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the final printed labeling or approved final labeling text to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

In addition, please note that this product has been approved **ONLY** for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

As such, please note that promotional statements or representations by you that this product may indeed be safe and efficacious in the treatment of diseases or patient populations beyond that contained in your approved labeling may be considered a violation of the Act. If you have any questions or concerns about this matter, please contact the Center for Drug Evaluation and Research's Division of Drug Marketing, Advertising, and Communications.

CHEMISTRY:

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80, 314.81, 314.520, 314.550, and 314.560.

If you have any questions, contact Nancy Chamberlin, Project Manager, at (301) 827-7410.

Sincerely,

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

Enclosure:
Labeling
Risk Management Program