DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020747/S-033

SUPPLEMENT APPROVAL

Cephalon, Inc
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Susan Franks, M.S.
Director, Regulatory Affairs

Dear Ms. Franks:

Please refer to your Supplemental New Drug Application (sNDA) dated December 5, 2011, received December 6, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACTIQ (fentanyl citrate) oral transmucosal lozenge.

We also acknowledge receipt of your amendments dated December 8 and 9, 2011; and your risk evaluation and mitigation strategy (REMS) assessment dated December 8, 2011.

This supplemental new drug application proposes modifications to the approved REMS for ACTIQ.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for ACTIQ was originally approved on July 20, 2011. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of changes to conform to the single shared REMS system developed for the transmucosal immediate-release fentanyl (TIRF) class of products**.**

Your proposed modified REMS, submitted on December 5, 2011, and appended to this letter, is approved.

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. The individual sponsors who are part of the single shared system are collectively referred to as TIRF sponsors. This single shared system, TIRF REMS Access program, includes the following products:

NDA 020747	Actiq (fentanyl citrate) oral transmucosl lozenge
NDA 021947	Fentora (fentanyl buccal tablets)
NDA 022266	Onsolis (fentanyl buccal soluble film)
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanyl) nasal spray
ANDA 077312	Fentanyl Citrate Oral Transmucosal Lozenge

Other products may be added in the future if additional NDAs or ANDAs are approved.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 20, 2011.

The revised REMS assessment plan should include, but is not limited to, the following:

1. **The TIRF REMS Access Program Outreach**

The following metrics will be tabulated for every reporting period to assess program outreach efforts:

a. Number of Dear HCP letters mailed to prescribers (by date)

b. Number of returned mailings of Dear HCP letters to prescribers

c. Number of Pharmacist letters mailed to pharmacies (by date)

d. Number of returned mailings of Pharmacist letters to pharmacies

2. The TIRF REMS Access Program Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and distributors, the following data will be tabulated for each reporting period and cumulatively:

a. Number of new patients enrolled by state

b. Number of patients inactivated

c. Number of new prescribers enrolled by state. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

d. Number of attempts needed for prescribers to successfully complete Knowledge Assessments, along with the method of completion utilized

e. Number of prescribers who are inactivated

f. Number of new pharmacies enrolled by type (inpatient or outpatient), by state. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

g. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments

h. Number of pharmacies that are inactivated by type (inpatient or outpatient)

i. Dispensing activity for enrolled outpatient pharmacies. Including,

   (1) Total number of prescriptions authorized

   (2) Total number of prescriptions denied and reasons for denial

      i. Number of prescriptions rejected for safety issues (description of safety issues and any interventions or corrective actions taken)

      ii. Number of prescriptions rejected for other reasons (e.g., prescriber not being enrolled)

j. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome)

k. Number of new distributors enrolled. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

l. Number of distributors inactivated, total

m. A histogram of the number of days between passive enrollment and receipt of a Patient-Prescriber Agreement Form. Stratify by the method of PPAF submission

n. A histogram of the number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment stratified by whether there is a PPAF in place.

3. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be tabulated for each reporting period and cumulatively:

a. Assessment of process for pharmacies to upgrade their pharmacy management systems (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems)

b. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem)

c. Call center report with

(1) Summary of frequently asked questions

(2) Problems reported

d. Description of corrective actions taken to address program/system problems.

e. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area

f. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays

The following reports for unintended system interruptions will be provided for each reporting period:

g. Reports identified of inadvertent enrollment deactivations

h. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code)

i. Reports of failure of re-enrollment notifications to reach stakeholders

j. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection.

4. Safety Surveillance

a. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures.

b. Surveillance data from the following sources will be included in the REMS Assessment Reports:

   (1) FDA AERS database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion

   (2) Other external databases.

5. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Survey results will be reported at 12 months and 24 months after the TIRF REMS Access program approval. TRIG will discuss with the FDA if additional surveys are needed after 24 months. The results from the surveys will be analyzed together with other REMS assessment data, and a report on any corrective actions taken and the outcome of those actions will be provided.

6. TIRF REMS Access Non-Compliance Plan

The TIRF Sponsors will implement a process for addressing stakeholder non-compliance in the program. The TRIG should provide the following in the first assessment:

a. A description of personnel that constitute the Non-Compliance Review Team

b. Describe how non-compliance information is collected and tracked to determine when the plan should be modified

If changes occur in any of the above information, it should be provided in subsequent assessments.

The TIRF sponsors should provide the following data regarding non-compliance in each assessment report:

a. Identify the number of non-compliant events.

b. Describe the non-compliant event and the corrective action measure taken.

c. Provide the outcome of the corrective action.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy.

We remind you that the requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 020747 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

Prominently identify any submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020747
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020747
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport. M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
12/28/2011