From: Raczkowski, Victor
Sent: Tuesday, August 22, 2006 9:13 AM
To: Marchione, Carol; Cansler, Kristen; Adams, Jessica; Diaz, Simon; Warner, Jamie
Subject: Immediate Action Needed: Final Version of Actiq RMP submission (to FDA on Tuesday August 22nd ASAP)
Attachments: Final Cover Letter for amend 3 to s-023 VR v1.doc; Actiq RMP 04 Nov 1998 Clean.pdf; Actiq RMP 09 Feb 1999 Clean.pdf; Actiq RMP 01 Aug 2001 Clean.pdf; Actiq RMP 09 Feb 1999 vs 04 Nov 1998.pdf; Actiq RMP 01 Aug 2001 vs 09 Feb 1999.pdf; Actiq RMP 16 Jan 2002 S009.pdf

Importance: High

Dear all,

I've attached a copy of the cover letter for the Actiq RMP and its attachments that need to go to FDA ASAP on Tuesday morning (we have a teleconference scheduled with FDA later on Tuesday afternoon).

Carol: I made substantial changes to your cover letter and chronology. Please review to ensure accuracy.

All: Carol is at the FENTORA launch meeting in Las Vegas and is several (three?) time zones behind us and may not see this until late morning Frazer time. **If you have not heard from Carol by 10:00 a.m. Frazer time (or earlier if you feel pressed) then please go forward with finalizing the document in the absence of her input**. Based on my review of the information in CentFile and CephDocs, I have sufficient confidence that the information provided is accurate, and while perhaps not optimal given the time constraints, the submission will be adequate to meet FDA's immediate needs.

I recognize that the approach of extracting documents (i.e., versions of the RMP and tracked-changes between successive RMPS) from previous submissions may not be optimal (e.g., modifications to these documents may have occurred during the review cycle). However, I was careful in the cover letter to describe these excerpts accurately as being from the submission (as opposed to saying with certainty that they were the approved documents). Again, I believe this is sufficient to meet FDA's immediate needs given the time constraints.

Kristen and Jessica: Please coordinate to have the submission published with appropriate links to the attachments. Please proofread for typos. Please send it by e-mail to FDA (Kim Compton) ASAP. Please indicate and ensure that a copy of the CD (or a hard copy or hard copies of the submission) are delivered to FDA by courier today.

Simon or Jamie: I will be at the dentist on Tuesday morning and should be back in the office by around 11:30 a.m. or noon; If I am not available to sign the letter, please sign on Carol's behalf.

Thank you.

Victor

Robert A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products, HFD-170
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

NDA 20-747
Actiq (Oral Transmucosal Fentanyl Citrate)
Amendment to S-023

Dear Dr. Rappaport,

Reference is made to our Prior-Approval Supplement (S-023) that was submitted to the Agency on March 5, 2006 to allow for a generic version of Actiq. The supplement contained proposals for generic labeling, a generic risk management plan (RMP), and a generic product description. Reference is also made to the August 9, 2006 teleconference with Dr. S. Hertz, Deputy Director of the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), and Ms. K. Compton, FDA Regulatory Health Project Manager for Actiq, during which the Agency stated that the currently approved RMP dated August 1, 2001 should be used as the basis for the generic RMP and during which Dr. Hertz requested that Cephalon submit a generic RMP showing deletion of the name "Actiq" throughout the document and replacement with "Oral Transmucosal Fentanyl Citrate." Finally, reference is made to an amendment to Supplement S-023 submitted on August 14, 2006 which included a proposed revised generic RMP meeting the criteria outlined in the August 9, 2006 teleconference

On August 18, 2006, FDA personnel contacted Cephalon to request a summary of the changes that have impacted the RMP since its initiation, including an annotated listing of each change. This submission provides a response to the Agency's request.
To address the Agency's request, we are providing the following items:

- **A chronology of the changes to the Actiq Risk Management Plan, organized by supplement, since its first approval on November 4, 1998 (see Attachment 1)**. As is evident upon reading the chronology, the approved supplements (S-003, S-008 and S-009) capture the changes to the RMP over time. However, for completeness and because they provide useful context, key communications between FDA and Cephalon about supplements pertaining to the RMP are summarized in the chronology regardless of their approval status.

  Comment [CI1]: Link to Attachment 1

- **Clean copies of the key versions of the Actiq Risk Management Plan**:
  - Version dated November 4, 1998

  Comment [CI2]: Link to "ACTIQ RMP 04 NOV 1998 CLEAN.pdf"

(Extracted from Anesta's submission dated February 10, 1999; S-003)
- Version dated February 9, 1999
(Extracted from Anesta's submission dated February 10, 1999; S-003)
- Version dated August 1, 2001
(Extracted from Cephalon's submission dated August 8, 2001; S-008)

Comment [CI3]: Link to "ACTIQ RMP 09 FEB 1999 CLEAN.pdf"

Comment [CI4]: Link to "ACTIQ RMP 01 AUG 2001 CLEAN.pdf"

- **Red-line/Strike-out versions of the Actiq Risk Management Plan showing the changes between successive key versions:**
  - Changes between Version dated February 9, 1999 and Version dated November 4, 1998
  (Extracted from Anesta's submission dated February 10, 1999; S-003)
  - Changes between Version dated August 1, 2001 and Version dated February 9, 1999
  (Extracted from Cephalon's submission dated August 8, 2001; S-008)

Comment [CI5]: Link to "ACTIQ RMP 09 FEB 1999 VS 04 NOV 1998.pdf"

Comment [CI6]: Link to "ACTIQ RMP 01 Aug 2001 VS 09 FEB 1999.pdf"

- **A copy of Cephalon's submission of January 16, 2002 (S-009)**

Comment [CI7]: Link to "ACTIQ RMP 16 JAN 2002 S009.pdf"

As is evident from the review of the *Chronology of FDA-Approved Changes to the Actiq Risk Management Program*, the key supplements impacting the RMP since its approval in 1998 are S-003, S-008, and S-009.

Comment [CI8]: Link to "Chronology of FDA-Approved Changes to the Actiq Risk Management Program in attachment 1

Cephalon has considered the RMP submitted under S-008 as the "currently approved" document. Because the changes approved under S-009 include a change in the name of the sales force as well as a revised letter indicating their responsibilities pertaining to the RMP, Cephalon believes that the RMP version of August 1, 2001, submitted under S-008, should therefore be revised to reflect the name "Pain Care Specialists" where the name of the sales force is specified. We have not provided a revised version of the RMP indicating this change with this amendment since the Agency may have additional comments that require further revisions. We can confirm this in forthcoming discussions with the Agency, such as the teleconference scheduled for August 22, 2006.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 738-6237.

Sincerely,

Carol S. Marchione
Sr. Director, Regulatory Affairs

ATTACHMENT 1

Chronology of FDA-Approved Changes to the Actiq Risk Management Program

(Organized by NDA Supplement)

1. **The initial Actiq RMP (RMP version dated November 4, 1998) was approved on November 4, 1998** as part of the approval action taken on the Actiq NDA submitted by Anesta Corp. (Anesta).[1]

2. **Anesta proposed revisions to the Actiq RMP in a submission dated February 10, 1999**. The proposed revisions reflected new information received from outside consultants, deletion of information deemed to be proprietary by Abbott Laboratories (e.g., the organizational structure within Abbott), and corrections relating to grammar and spelling. Some of the key revisions included (a) changes to the Carton--Back Panel Text (e.g., moving text without changing the content and updating the pharmacist checklist), (b) changes to the Child-resistant Lock (e.g., change from a magnetic cabinet lock to a plastic latch/lock, known as a "double-lock"), (c) correction of a statement about the reading level of the Children's Booklet, and (d) revisions to reflect current procedures at Abbott Laboratories for adverse event investigation and follow–up. **FDA approved the revised RMP (RMP version dated February 9, 1999) on March 26, 1999 under S-003**.

3. In a correspondence to the NDA dated October 18, 1999, Anesta submitted a revised RMP (RMP version dated October 18, 1999) to reflect the currently approved version of the package insert. The content of the revised RMP was identical to the approved February 9, 1999 version of the RMP with the exception of Attachment 5 (i.e., the Actiq package insert). Thus, the RMP was changed only by substituting the currently approved package insert in Attachment 5 of the RMP for the outdated package insert.

4. **In a correspondence dated May 31, 2000, Anesta filed proposed changes to the RMP (RMP version dated May 26, 2000) under S-007 to reflect recent changes in responsibility for the sales and marketing of Actiq in the United States**. The submission indicated that Anesta had responsibility for the sales and marketing of Actiq in the U.S. and that Abbott would continue to manufacture and distribute Actiq in the U.S. Although initially a joint effort between Anesta

[1] On October 10, 2000, Anesta Corp of Salt Lake City, Utah became a wholly owned subsidiary of Cephalon Inc.

and Abbott Laboratories, the RMP would now be the sole responsibility of Anesta.

On October 1, 2001, FDA issued a not approvable letter for S-007. Cephalon subsequently responded to the identified deficiencies in a submission dated October 26, 2001, Cephalon. In its response, Cephalon noted that because of the change in ownership of Actiq, the proposed May 26, 2000 version of the RMP was now obsolete. Cephalon indicated that the RMP would be revised to acknowledge the change in ownership of Actiq and to incorporate the Agency's comments to S-007 where still relevant while reflecting Cephalon's current practices. No response was received by Cephalon to its October 26, 2001 communication.

5. **In a Cephalon submission dated August 8, 2001 (S-008)[2], Cephalon submitted a proposed revised RMP (RMP version dated August 1, 2001) to FDA as part of a prior-approval supplement**. The supplement provided for (a) a transfer of the manufacturing site for the U.S. Actiq market from Abbott, North Chicago to Cephalon Salt Lake City Operations; and (b) a change in the drug product formulation from the cooked-sugar product to a compressed matrix product. More specifically, the sNDA provided for changes of the supplier, manufacturing process and regulatory specifications of the drug substance; as well as for changes in the formulation, manufacturing process, facilities, regulatory specifications and test methods, and container and labeling of the drug product. Consequently, the submission included proposed changes to the packaging, labeling, and RMP. **FDA approved S-008 on February 19, 2003.**

6. **In a prior-approval supplement dated January 16, 2002 (S-009), Cephalon addressed a comment in the Agency's not approvable letter for Supplement S-007**. Specifically, Cephalon responded to the Agency's concern over the name of the sales force as reflected in section 5.2 (The Oncology Specialist) of the RMP. The submission included a proposal to name the individuals in this sector of the sales force "Pain Care Specialists." It also included proposed revisions to a letter that the company sends to the Sales Specialists, which outlines their responsibilities pertaining to the RMP. **On January 29, 2003, FDA approved S-009** changing the name used to refer to the portion of the sales force that markets the drug product.

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[2] Cephalon's August 8, 2001 submission (S-008) should not be confused with Anesta's submission of May 31, 2000 (S-007). The Cephalon submission dated August 8, 2001 was designated initially by Cephalon as Supplement S-007. However, FDA's letter dated September 24, 2001 acknowledging receipt of the submission referred to it as Supplement S-008. Consequently Cephalon subsequently began to refer to the August 8, 2001 submission as Supplement S-008 in accordance with FDA's designation.

6. **On November 22, 2004, Cephalon submitted a proposal to revise the RMP (S-020).** The purpose was to provide more clear and concise text, to delete the launch activities described in the original document, to more accurately describe the RMP processes as adopted by Cephalon, and to emphasize the three key safety messages of the RMP even more clearly. **On June 21, 2005, FDA issued a not approvable letter for S-020**.

   On January 6, 2006, Cephalon amended S-020 to address the deficiencies identified in the Agency's not approvable letter. Noting that the review of the entire application is not complete, FDA issued comments to Cephalon on July 24, 2006 on S-020 which had been provided by the Office of Surveillance and Epidemiology (OSE) and the Controlled Substances Staff (CSS). An FDA action on the amended supplement S-020 is pending.

FDA APPROVED RMP
(November 4, 1998)

Note: The Attached RMP Was Included In The November 4, 1998 Facsimile From FDA (See November 4, 1998 Approval Letter)

Actiq®

(oral transmucosal fentanyl citrate)

Risk Management Program

(November 4, 1998)

NDA Number: 20-747

Sponsor:

Anesta Corp.
4745 Wiley Post Way
Plaza 6, Suite 650
Salt Lake City, UT 84116
801-595-1405

Marketing Partner:

Abbott Laboratories
Hospital Products Division
Abbott Park, IL 60064

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TABLE OF CONTENTS

1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1) accidental ingestion of *Actiq* by children

2) improper patient selection (prescriptions to and usage by opioid non-tolerant patients)

3) diversion or abuse

Anesta Corp. and Abbott Laboratories have designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- *Actiq*'s CII status

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portions of this RMP should be used in a promotional context or used to promote Actiq in a manner inconsistent with the product label.

The Risk Management Plan and all of its components will be fully operational at the time of launch.

1.1 Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children
  - *Actiq* could be harmful or fatal to a child if accidentally ingested
  - *Actiq* must be properly stored and handled
  - *Actiq* must be properly disposed of after use
  - Healthcare professionals must counsel patients on child safety messages
  - Accessible and easily understood directions on what to do in case of accidental ingestion
- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - Actiq is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients.
- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

2.0 Product Definition

The Actiq unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a raspberry-flavored lozenge on a handle (See Figure 1).
Actiq provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that Actiq may be perceived as a lollipop. Because of the design of the Actiq unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

2.1 *Actiq* unit

The *Actiq* unit consists of an opaque, white to off-white drug matrix that has been opacified and colored to make it look less appealing to children. Its handle has been designed with a "paddle" with a molded "Rx" in the center to identify it as a product for medical use. Additionally, on the backside of the paddle the word "fentanyl" is clearly visible.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use). The handle carries legible, laser-engraved product identification information (microgram content of active drug , product code, manufacturer logo, and "fentanyl") in 9 point, charcoal-gray type on a pure white background. The laser-engraved imprint on the handle is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning.

Insert Figure 1

2.2 *Actiq* Child-Resistant Pouch

- See Figures 2 and 3.
- Each *Actiq* unit is individually sealed in its own child-resistant pouch. The Actiq pouch is made of a heavy, multi-layer laminated foil material and requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a 99% effectiveness rating, exceeding the 80% requirement.
- Individual child-resistant packaging (one dosage unit in each pouch) is intended to minimize exposure by limiting access to just one unit at a time.
- The pouch is opaque. A child cannot see the unit when it is in its pouch. The pouch does not resemble food or most candy wrappers.
- The dosage strength of each unit is marked on each handle, on the foil pouch, and shelf carton. The colors are a secondary aid in product identification:

Gray	200 mcg

Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

- The front of each pouch utilizes an icon to draw attention to warnings about child safety and opioid tolerance, standard product identification information is also included on the front of the pouch. The back of each pouch contains the same icon, plain-language warnings about child safety and proper product storage, and a reminder to read the *Actiq* Patient Leaflet.

- The front of each pouch contains the CII symbol, a "May be habit forming" warning and an "Rx only" warning.

Insert Figures2

Insert Figure 3

2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Figures 4, 6 pages). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.

- The right hand side of the back of the shelf carton contains a designated location for the application of the pharmacy-dispensing label. A checklist for the pharmacist is included in this space. The checklist reminds the pharmacist to make sure the patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet, and to discuss the *Actiq* Welcome Kit. Below this space are prominent instructions on what to do in case of an accidental exposure. On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units, and a reminder to read the *Actiq* Patient Leaflet. On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet.

- At the initiation *of Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200-mcg units. At each new dose of *Actiq* during titration, it

is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

- The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in similar fashion.

- Each shelf carton contains eight strips of three pouches, for a total of 24 pouches of a single strength of *Actiq*. The shelf carton represents approximately a ten-day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

Insert Figure 4

Insert figure 5-1

Insert figure 5-2

Insert figure 5-3

Insert figure 5-4

2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf carton to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for titration and prescribing.

2.4.1 Multiple Dosage Strengths

Actiq will be made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed.*

2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

3.0 Labeling

3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)
- 100% drug accountability by individual count is required
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to ensure a legitimate medical purpose before dispensing

Actiq's status as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to

the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and three copies will be packaged in every shelf carton (RMP Attachment 1). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *ACTIQ* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.
- The *ACTIQ* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized "walk through" of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call 1-800 Poison Control if the patient or child is awake
  - instructions for care of the patient or child who is having trouble breathing or not breathing at all
- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word "must" is used instead of the word "should". The warning language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid pain medicines . . ." is used.

3.3 Package Insert

The *Actiq* Package Insert (PI) [See RMP Attachment 2], clearly and explicitly communicates messages about child safety, proper patient selection and prevention of diversion and abuse (RMP Attachment 3). The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- Indication: Actiq is indicated 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.

- Black box warnings:

  PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.
  Actiq is indicated 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. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

  Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ***Actiq*** is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

  Actiq is intended to be used only in the care of cancer patients only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

  Patients and their caregivers must be instructed that ***Actiq*** contains a medicine in an amount that can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

- Titration instructions which minimize the number of units in the home

- Detailed safe home handling and storage

- Detailed instructions for disposal of used and unused units

- CII designation

4.0 Professional Medical Education

Anesta and Abbott will work in conjunction with FDA (through the office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to Actiq.

4.1 Key Message Points

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages have been described earlier in section 1.1 of this RMP:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product
- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, will be provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

4.2 Breakthrough Cancer Pain Nursing Medical Education Monograph

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

4.3 The *Actiq* Speakers Bureau / Medical Education Programs

Prior to product launch, Anesta and Abbott will formally train the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment 2):

- Approximately 50 prominent physician educators in pain management
- Approximately 50 prominent nurse educators in pain management
- Approximately 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional and national settings.

4.4 Publications

Anesta and Abbott will publish articles, in peer-reviewed journals, messages that will re-enforce elements of this RMP. The publications selected are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

4.4.1 Broad-Based Publications

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)
- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

4.4.2 Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. Abbott and Anesta will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, Anesta will contact these publications to request increased emphasis on the RMP elements.

4.4.3 Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

4.4.4 Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

4.4.5 Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)
- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000 +)
- Journal of Managed Care Pharmacy (circulation 40,000+)

4.4.6 Pharmacy Newsletters (Print and Electronic)

Abbott and Anesta will incorporate the *Actiq* key safety messages and new product reviews into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS 4,000 stores
  - Rite Aid 3,000 stores
  - Walgreens 2,200 stores

- State board of pharmacy newsletters

4.5 Communication with DEA

Information on proper disposal of Actiq will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

5.0 *Actiq* Launch Program

Actiq will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.
All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients. Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.
Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

5.2 The *Actiq* Specialist (Abbott Sales Organization)

Abbott will place approximately 40 full time *Actiq* Specialists in the field to personally call on the target audience. The *Actiq* Specialists will be the primary, day to day link to the physicians, nurses and pharmacists who will be using the product. The *Actiq* Specialists will play a key role in implementing the RMP.

- Each *Actiq* Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with four home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by two weeks of in-house training at Abbott corporate headquarters and at least one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and Abbott expectations regarding sales activity in the field. Importantly, *Actiq* Specialists will be tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the *Actiq* Specialists will personally call on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they will educate the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies will be called on by the *Actiq* Specialist in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group will be offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These programs will all provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of Actiq to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. The letter must have FDA review and prior approval before issue. Moreover, the compensation program for *Actiq* Specialists will direct them to promote into only the target audience.
In their personal calls to physicians, nurses, and pharmacists, the *Actiq* Specialist will demonstrate a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use.

5.3 Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

5.4 Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

5.4.1 *Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including.

- *Actiq* Package Insert and *Actiq* Patient Leaflet
- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

5.4.2 The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* Internet site for more information. The letter must have FDA review and prior approval before issue.

5.4.3 The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

5.4.4 Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5 Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5.1 *Actiq* CD ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in RMP Attachment 7. This program will be available via mass direct mail, the *Actiq* Specialist and the *Actiq* Internet site.

5.5.2 *Actiq* Internet Site

An *Actiq* Internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

5.5.3 Emergency 911

This number will be prominently featured in all patient education and promotional materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the patient or child is not awake and alert or is breathing slowly.

5.5.4 Central 1-800 Poison Control Number

A single 1-800-telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in all patient education and promotional materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the patient is awake and alert.

6.0 Patient and Caregiver Education

6.1 The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a magnetic lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Figure 7).
- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (Figure 8).

- Child -Resistant Storage container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (Figure 9). Temporary storage containers will be available at the point of dispensing whenever and wherever Actiq is dispensed.

- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.
Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet.
Target pharmacists will be given an *Actiq* Welcome Kit by an *Actiq* Specialist and briefed on how patients can obtain them.
Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet --will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.

Insert Figure 7

Insert Figure 8

Insert Figure 9

6.2 Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages
- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the *Actiq* Specialist or 1-800 number. This video will be available in either English or Spanish.
All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

6.3 Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

6.4 Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed. to be read and be understood by younger children will be distributed. This book has been developed at a 2nd to 3rd grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

7.0 POINT OF DISPENSING INTERVENTIONS

The following activities will be implemented at all *Actiq* points of dispensing. Product samples will not be made available.

7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, Actiq warnings will be placed in the major commercial pharmacy precaution software systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.
Examples of pharmacist warning screens and electronically produced patient information sheets are provided as RMP Attachment 7.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an *Actiq* Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the Abbott *Actiq* Specialists and be made available to any pharmacist upon request. The package and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (e.g. the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.)

7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever Actiq is dispensed.

8.0 Surveillance Goals and Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, Anesta/Abbott will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1 Direct Patient Feedback

8.1.1 Rite-Aid / Eckerd call back system

A callback system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include Rite-Aid, Eckerd. Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, Rite-Aid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

8.2 Prescription Monitoring

8.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of this data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. This data provides the prescriber's name, the physician specialty and zip code. This data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties

such as surgeons (inappropriate patient selection). Abbott will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

8.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached as RMP Attachment 6. These data will be reported to the FDA on a quarterly basis as described in section 10.0.

8.2.3 Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

Through its chargeback system, Abbott will receive information on retail pharmacy sales from drug wholesalers. This information will be shared with the *Actiq* Specialist. The *Actiq* Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months an Abbott Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will reinforce appropriate product usage and confirm the accuracy of the high-volume *Actiq* pharmacy listing on which the *Actiq* Specialists are visiting. Information from the Abbott Trade Specialists' meetings with wholesalers will be shared with the *Actiq* Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

8.3 Adverse Events

8.3.1 Abbott Standard Operating Procedure

Abbott has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.
A toll free number will be staffed to receive adverse events reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representives or others. All reports are logged into a computer database and investigated.
All serious events, as defined by current federal regulations, receive immediate investigation and follow-up by Abbott. The details of this procedure are summarized below.

a) The incident report is reviewed by the *Actiq* Incident Review Team and an action plan is developed. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.
b) An investigation team is assigned and contact made with the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.
c) The investigation team report conclusions are reported to the Incident Review Team, which consults with senior management to determine if corrective action should be recommended and/or taken.

A schematic of the Incident Review Team and process is attached as RMP Attachment 7.

8.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert".
- 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 experiences is unexpected, will be processed and reported to the FDA as a "15 day Alert".
- Any serious adverse drug experience which 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 experiences is unexpected, will be processed and reported to the FDA as a "15 day Alert".

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert Report," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (eg., call-in, literature, poison control centers, etc).

8.3.3 Literature Monitoring

In addition to specific event reporting, Abbott maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. (Any significant findings will be included in the quarterly report (as per 21 CFR § 314.80).

8.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

8.4.1 Central 1-800 Poison Control Number

A single 1-800-telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be highly publicized in all patient education materials. (Any significant findings will be included in the quarterly report (as per 21 CFR § 314.80).

8.4.2 Toxic Exposures Surveillance System (TESS)

TESS reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. This data is available once yearly and will be included in the analysis for FDA quarterly reports.

8.5 Abuse

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

8.5.1 Routine Abbott Interaction with DEA

Abbott Laboratories Corporate Regulatory Affairs maintains a proactive program to identify possible product diversion. Abbott routinely visits DEA District offices with jurisdiction over Abbott distribution facilities to review information on the potential "street use" of Abbott products. In addition, an interactive relationship has been developed so that Abbott is alerted to specific instances. Any incident is investigated and resolved in conjunction with the DEA and state drug control authorities.

8.5.2 Abbott Exceptions System

Actiq will be added to Abbott's exception reporting system to the DEA. Under this system, any orders that exceed the norm by two or more standard deviations are reported to the DEA for follow-up and investigation.

8.5.3 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospitals EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports

DAWN This database will also be monitored to identify issues, which have not surfaced through standard DEA interactions.

8.5.4 State Drug Control Authorities or State Boards of Pharmacy

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

8.6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that *Actiq* Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the *Actiq* specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted focused launch/promotional plan.

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1) A letter from Abbott's Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection The letter must have FDA revisions and approval before it is issued.

2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an *Actiq* Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly Actiq prescriptions, Abbott will contact the appropriate professional society (i.e. American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total Actiq prescriptions for 2 additional quarters, an aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

9.2 Accidental Ingestion

In the event of a serious child poisoning report, Abbott will initiate the standard operating procedure for adverse events detailed in section 8.3.1 of this RMP and in RMP Attachment 7.

10.0 FDA REPORTING

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day "Alert Reports" (See Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these "15-day Alert reports" will be sent to Surveillance and Monitoring (OPDRA) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

Anesta / Abbott will provide a quarterly report to the FDA compiled from all data collected by the methods described under the Actiq Surveillance and Monitoring Program and Interventions (see Section 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. Anesta/Abbott will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the Actiq Risk Management Plan. This report will be provided as part of the Actiq quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

ATTACMENTS

RMP 1 *Actiq* Patient Leaflet

RMP 2 *Actiq* Package Insert

RMP 3 Elements of RMP to be Included in Speaker Bureau Training

RMP 4 *Actiq* CD ROM schematic

RMP 5 Pharmacy Computer Warning screens

RMP 6 IMS National Disease and Therapeutic Index example page

RMP 7 Incident Team schematic

Actiq®

(oral transmucosal fentanyl citrate)

Risk Management Program

(February 9, 1999)

NDA Number: 20-747

Sponsor:

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19- 002

February 9, 1999

TABLE OF CONTENTS

1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1. accidental ingestion of *Actiq* by children
2. improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3. diversion or abuse

Anesta Corp. and Abbott Laboratories have designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- CII status for *Actiq*

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portions of this RMP should be used in a promotional context or used to promote *Actiq* in a manner inconsistent with the product label.

The RMP and all of its components should be fully operational at the time of launch.

1.1 Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children
  - *Actiq* could be harmful or fatal to a child if accidentally ingested

- *Actiq* must be properly stored and handled
- *Actiq* must be properly disposed of after use
- Healthcare professionals must counsel patients on child safety messages
- Accessible and easily understood directions on what to do in case of accidental ingestion

- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for use in acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - *Actiq* is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients

- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

2.0 Product Definition

The *Actiq* unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a raspberry-flavored lozenge on a handle (see Attachment 1). *Actiq* provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that *Actiq* may be perceived as a lollipop. Because of the design of the *Actiq* unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

2.1 *Actiq* Unit

The *Actiq* unit consists of an opaque, white to off-white drug matrix that has been opacified and colored to make it look less appealing to children. Its handle has been designed with a "paddle" with a molded "Rx" in the center to identify it as a product for medical use. Additionally, on the back side of the paddle the word "fentanyl" is clearly visible.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use). The handle carries legible, laser-engraved product identification information (ie, microgram content of active drug, product code, Abbott logo, and "fentanyl") in 9 point, charcoal-gray type on a pure

white background. The laser-engraved imprint on the handle is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning.

2.2 *Actiq* Child-Resistant Pouch

Each *Actiq* unit is individually sealed in its own child-resistant pouch. The *Actiq* pouch is made of a heavy, multi-layer laminated foil material and requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a 99% effectiveness rating, exceeding the 80% requirement.

Individual child-resistant packaging (one dosage unit in each pouch) is intended to minimize exposure by limiting access to just one unit at a time.

The pouch is opaque. A child cannot see the unit when it is in its pouch. The pouch does not resemble food or most candy wrappers.

The dosage strength of each unit is marked on each handle, and on the foil pouch and shelf carton. The colors are a secondary aid in product identification.

Gray	200 mcg
Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

The front of each pouch utilizes an icon to draw attention to warnings about child safety and opioid tolerance, standard product identification information is also included on the front of the pouch (see Attachment 2). The back of each pouch contains the same icon, plain-language warnings about child safety and proper product storage, and a reminder to read the *Actiq* Patient Leaflet.

The front of each pouch contains the CII symbol, a "May be habit forming" warning, and an "Rx only" warning.

2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Attachment 3). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.

- The right hand side of the back of the shelf carton contains a designated location for the application of the pharmacy-dispensing label. A checklist for the pharmacist is included in this space. The checklist reminds the pharmacist to make sure the

patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet, to discuss the *Actiq* Welcome Kit, and to counsel the patient about disposal of partially consumed units.

- On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units, a reminder to read the *Actiq* Patient Leaflet, and prominent instructions on what to do in case of an accidental exposure.

- On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet .

At the initiation of *Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200 mcg units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in a similar fashion.

Each shelf carton contains eight strips of three pouches, for a total of 24 pouches of a single strength of *Actiq*. The shelf carton represents approximately a ten day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf cartons to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for prescribing.

2.4.1 Multiple Dosage Strengths

Actiq will be made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed.*

2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

3.0 Labeling

3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)
- strict accountability of finished units
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to check for a legitimate medical purpose before dispensing

The status of *Actiq* as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and four copies will be packaged in every shelf carton (see Attachment 4). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *Actiq* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.

- The *Actiq* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized "walk through" of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call Poison Control at 1-800-690-3924 if the patient or child is awake
  - instructions for care of the patient or child who is having trouble breathing or not breathing at all
- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word "must" is used instead of the word "should." The warning language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines..." is used.

3.3 Package Insert

The *Actiq* Package Insert (PI) clearly and explicitly communicates messages about child safety, proper patient selection, and prevention of diversion and abuse (see Attachment 5). These messages (see Attachment 6) are important elements of the RMP. The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- Indication: *Actiq* is indicated 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.
- Black box warnings, which are:

  PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

  ***Actiq* is indicated 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.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ***Actiq*** is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

- Titration instructions which minimize the number of units in the home
- Detailed safe home handling and storage
- Detailed instructions for disposal of used and unused units
- CII designation

4.0 Professional Medical Education

Anesta and Abbott will work in conjunction with FDA (through the Office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to *Actiq*.

4.1 Key Message Points

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages, which have been described earlier in section 1.1 of this RMP, include:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product

- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, will be provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

4.2 Breakthrough Cancer Pain Nursing Medical Education Monograph

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

4.3 The *Actiq* Speakers Bureau / Medical Education Programs

Prior to product launch, Anesta and Abbott will formally train the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment 6):

- At least 50 prominent physician educators in pain management
- At least 50 prominent nurse educators in pain management
- At least 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional, and national settings.

4.4 Publications

Manuscripts will be submitted to peer-reviewed journals for consideration. They will include messages that reinforce elements of this RMP. The manuscripts selected for publication are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

4.4.1 Broad-Based Publications

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (circulation 10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)

- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

4.4.2 Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses, and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. Abbott and Anesta will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, Anesta will contact these publications to request increased emphasis on the RMP elements.

4.4.3 Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

4.4.4 Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

4.4.5 Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)

- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000+)
- Journal of Managed Care Pharmacy (circulation 40,000+)

4.4.6 Pharmacy Newsletters (Print and Electronic)

Abbott and Anesta will request that the *Actiq* key safety messages and new product reviews be incorporated into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS 4,000 stores
  - RiteAid 3,000 stores
  - Walgreens 2,200 stores
- State board of pharmacy newsletters

4.5 Communication with DEA

Information on proper disposal of *Actiq* will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

5.0 *Actiq* Launch Program

Actiq will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.

All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients.

Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.

Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

5.2 The Oncology Specialist (Abbott Sales Organization)

Approximately 40 full time Oncology Specialists will be placed in the field to personally call on the target audience. The Oncology Specialists will be the primary day to day link to the physicians, nurses and pharmacists who will be using the product. The Oncology Specialists will play a key role in implementing the RMP.

Each Oncology Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with four home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by two weeks of in-house training at Abbott corporate headquarters and at least one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and Abbott expectations regarding sales activity in the field. Importantly, Oncology Specialists will be tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the Oncology Specialists will personally call on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they will educate the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies will be called on by the Oncology Specialist in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group will be offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These programs will provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of *Actiq* to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. The letter must have FDA review and prior approval before issue. Moreover, the compensation program for Oncology Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the Oncology Specialist will discuss a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD-ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use.

5.3 Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

5.4 Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

5.4.1 *Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including:

- *Actiq* Package Insert and *Actiq* Patient Leaflet
- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD-ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

5.4.2 The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* internet site for more information. The letter must have FDA review and prior approval before issue.

5.4.3 The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

5.4.4 Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5 Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5.1 *Actiq* CD-ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in Attachment 7. This program will be available via mass direct mail, the Oncololgy Specialist and the *Actiq* internet site.

5.5.2 *Actiq* Internet Site

An *Actiq* internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

5.5.3 Emergency 911

This number will be prominently featured in all patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the person (eg, a child) is not awake and alert or is breathing slowly.

5.5.4 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the person (eg, a child) is awake and alert.

6.0 Patient and Caregiver Education

6.1 The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Attachment 8).
- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (Attachment 9).
- Child-Resistant Temporary Storage Container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (Attachment 10). Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.
- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet. Target pharmacists will be given an *Actiq* Welcome Kit by an Oncology Specialist and briefed on how patients can obtain them.

Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet -- will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.

6.2 Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages
- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the Oncology Specialist or 1-800 number. This video will be available in either English or Spanish.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

6.3 Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

6.4 Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed., to be read and to be understood by younger children will be distributed. This book has been developed at a 2nd to 4th grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

7.0 Point Of Dispensing Interventions

The following activities will be implemented at the *Actiq* points of dispensing. Product samples will not be made available.

7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, vendors of major commercial pharmacy precaution software will be asked to place *Actiq* warnings in their systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.

Examples of pharmacy warning screens and electronically produced patient information sheets are provided as Attachment 11.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an Oncology Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the Abbott Oncology Specialists and be made available to any pharmacist upon request. The package (eg, back panel of shelf carton) and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (eg, the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.

7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.

8.0 Surveillance Goals And Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, Abbott/Anesta will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1 Direct Patient Feedback

8.1.1 Chain Pharmacy Call Back System

A call back system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include RiteAid, Eckerd, Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, RiteAid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

8.2 Prescription Monitoring

8.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of this data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. These data provide the prescriber's name, the physician specialty and zip code. These data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). Abbott will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

8.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached (see Attachment 12). These data will be reported to the FDA on a quarterly basis as described in section 10.0.

8.2.3 Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

Abbott will receive information on retail pharmacy sales. This information will be shared with the Oncology Specialist. The Oncology Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months an Abbott Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will request information on any additional pharmacies which need to be added to the list. Information from the Abbott Trade Specialists' meetings with wholesalers will be shared with the Oncology Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

8.3 Adverse Events

8.3.1 Abbott Standard Operating Procedure

Abbott has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.

A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated.

Any adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by Abbott. The details of this procedure are summarized below.

a) The incident report is reviewed by an investigation team, and an investigation is initiated. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.

b) The medical experience analyst assigned contacts the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.

c) The medical investigation conclusions are discussed with Anesta to determine reportability.

8.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of diversion (ie, use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of "off label use" (ie, that is used outside of the approved indication for *Actiq*) whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert report ," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (eg, call-in, literature, poison control centers, etc).

8.3.3 Literature Monitoring

In addition to specific event reporting, Abbott maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

8.4.1 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. These data are available once yearly and will be included in the analysis for FDA quarterly reports.

8.5 Abuse

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

8.5.1 Routine Abbott Interaction with DEA

Abbott Laboratories Corporate Regulatory Affairs maintains a proactive program to identify possible product diversion. Abbott routinely visits DEA District offices with jurisdiction over Abbott distribution facilities to review information on the potential "street use" of Abbott products. In addition, an interactive relationship has been developed so that Abbott is alerted to specific instances. Abbott will cooperate with DEA and state drug control authorities' investigations, as requested.

8.5.2 Abbott Exceptions System

Actiq will be added to Abbott's exception reporting system to the DEA. Under this system, any orders that exceed the norm by two or more standard deviations are reported to the DEA for follow-up and investigation.

8.5.3 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

8.5.4 State Drug Control Authorities or State Boards of Pharmacy

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

8.6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that Oncology Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the Oncology Specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted, focused launch/promotional plan.

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1) A letter from Abbott's Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA review and approval before it is issued.

2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an Oncology Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly *Actiq* prescriptions, Abbott will contact the appropriate professional society (ie, American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total *Actiq* prescriptions for two additional quarters, an aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

9.2 Accidental Ingestion

In the event of an unintended pediatric exposure, Abbott will initiate their standard operating procedure for adverse events detailed in section 8.3.1 of this RMP.

10.0 FDA Reporting

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day Alert reports (see Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these 15–day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

Anesta/Abbott will provide a quarterly report to the FDA compiled from all data collected by the methods described under the *Actiq* Surveillance and Monitoring Program and Interventions (see Sections 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. Anesta/Abbott will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the *Actiq* Risk Management Plan. This report will be provided as part of the *Actiq* quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

List of Attachments

1 *Actiq* Dosage Unit (example: 200 mcg)

2 Labeling - Foil Pouch (example: 400 mcg)

3 Labeling - Shelf Carton (example: 400 mcg)

4 *Actiq* Patient Leaflet

5 *Actiq* Package Insert

6 Elements of RMP to be Included in Speaker Bureau Training

7 *Actiq* CD-ROM Schematic

8 Child Safety Lock

9 Secure Personal Container (ie, "fanny pack")

10 Child-resistant Temporary Storage Container

11 Pharmacy Computer Warning screens

12 IMS National Disease and Therapeutic Index example page

Actiq®

(oral transmucosal fentanyl citrate)

Risk Management Program

August 1, 2001

NDA Number: 20-747

Sponsor:

Anesta Corp.,
a Subsidiary of
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380

TABLE OF CONTENTS

1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1. accidental ingestion of *Actiq* by children
2. improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3. diversion or abuse

Anesta Corporation, a subsidiary of Cephalon, Inc. has designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- CII status for *Actiq*

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portion of this RMP should be used in a promotional context or used to promote *Actiq* in a manner inconsistent with the product label.

The RMP and all of its components should be fully operational at the time of launch.

1.1 Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children
  - *Actiq* could be harmful or fatal to a child if accidentally ingested
  - *Actiq* must be properly stored and handled
  - *Actiq* must be properly disposed of after use
  - Healthcare professionals must counsel patients on child safety messages
  - Accessible and easily understood directions on what to do in case of accidental ingestion
- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for use in acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - *Actiq* is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients
- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

2.0 Product Definition

The *Actiq* unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a berry-flavored lozenge on a handle (see Attachment 1). *Actiq* provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that *Actiq* may be perceived as a lollipop. Because of the design of the *Actiq* unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

2.1 *Actiq* Unit

The *Actiq* unit consists of an opaque, white to off-white solid drug matrix that appears medicinal to make it look less appealing to children. The solid drug matrix and the tag at the end of the handle indicate the dosage strength. The handle tag is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning. A yellow triangle icon is also imprinted on the handle tag as a reminder of the child safety precautions.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use).

2.2 *Actiq* Child-Resistant Blister Package

Each *Actiq* unit is individually sealed in its own child-resistant blister package. This blister package is made of thick PVC/Aclar blister packaging material with a strongly sealed foil/paper lidding that requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a 100% effectiveness rating, exceeding the 80% requirement.

Individual child-resistant packaging (one dosage unit in each blister package) is intended to minimize exposure by limiting access to just one unit at a time.

The blister package is opaque so that a child cannot see the unit when it is in the blister package. The blister package does not resemble food or candy wrappers.

The dosage strength of each unit is marked on the solid drug matrix, on each handle tag, on the blister package and on the shelf carton. The handle tags, blister packages and cartons have colored markings that are a secondary aid in product identification.

Gray	200 mcg
Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

The blister package utilizes an icon to draw attention to warnings about child safety and opioid tolerance and standard product identification information. (see Attachment 2). It also contains a reminder to read the *Actiq* Patient Leaflet. In addition the blister package label contains the CII symbol, a "May be habit forming" warning, and an "Rx only" warning.

2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Attachment 3). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.

- The back of the shelf carton contains a checklist for the pharmacist. The checklist reminds the pharmacist to make sure the patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet, to discuss the *Actiq* Welcome Kit, and to counsel the patient about disposal of partially consumed units.

- On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units, a reminder to read the *Actiq* Patient Leaflet, and prominent instructions on what to do in case of an accidental exposure.

- On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet.

At the initiation of *Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200 mcg units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in a similar fashion.

Each shelf carton contains ten strips of three blister packages, for a total of 30 blister packages of a single strength of *Actiq*. Each carton will also include five patient leaflets and one package insert. The shelf carton represents approximately a ten day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf cartons to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for prescribing.

2.4.1 Multiple Dosage Strengths

Actiq is made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed*.

2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

3.0 Labeling

3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)
- strict accountability of finished units
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to check for a legitimate medical purpose before dispensing

The status of *Actiq* as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and five copies will be packaged in every shelf carton (see Attachment 4). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *Actiq* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.
- The *Actiq* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized "walk through" of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call Poison Control at 1-800-690-3924 if the patient or child is awake

- instructions for care of the patient or child who is having trouble breathing or not breathing at all

- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word "must" is used instead of the word "should." The warning language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines..." is used.

3.3 Package Insert

The *Actiq* Package Insert (PI) clearly and explicitly communicates messages about child safety, proper patient selection, and prevention of diversion and abuse (see Attachment 5). These messages (see Attachment 6) are important elements of the RMP. The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- Indication: *Actiq* is indicated 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.
- Black box warnings, which are:

> **PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.**
>
> ***Actiq* is indicated 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.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.
>
> Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ***Actiq*** is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.
>
> *Actiq* is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

- Titration instructions which minimize the number of units in the home
- Detailed safe home handling and storage
- Detailed instructions for disposal of used and unused units
- CII designation

The *Actiq* insert will be included in each shelf carton.

4.0 Professional Medical Education

Cephalon, Inc. will work in conjunction with FDA (through the Office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to *Actiq*.

4.1 Key Message Points

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages, which have been described earlier in section 1.1 of this RMP, include:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product
- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, are provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

4.2 Breakthrough Cancer Pain Nursing Medical Education Monograph

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

4.3 The *Actiq* Speakers Bureau / Medical Education Programs

Prior to product launch, Anesta and Abbott formally trained the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment 6):

- At least 50 prominent physician educators in pain management
- At least 50 prominent nurse educators in pain management
- At least 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional, and national settings.

4.4 Publications

Manuscripts will be submitted to peer-reviewed journals for consideration. They will include messages that reinforce elements of this RMP. The manuscripts selected for publication are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

4.4.1 Broad-Based Publications

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (circulation 10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)

- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

4.4.2 Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses, and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. Cephalon, Inc. will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, Cephalon, Inc. will contact these publications to request increased emphasis on the RMP elements.

4.4.3 Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

4.4.4 Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

4.4.5 Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)

- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000+)
- Journal of Managed Care Pharmacy (circulation 40,000+)

4.4.6 Pharmacy Newsletters (Print and Electronic)

During the initial launch of Actiq, requests were made that the *Actiq* key safety messages and new product reviews were to be incorporated into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS 4,000 stores
  - RiteAid 3,000 stores
  - Walgreens 2,200 stores
- State board of pharmacy newsletters

4.5 Communication with DEA

Information on proper disposal of *Actiq* will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

5.0 *Actiq* Launch Program

Actiq will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.

All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients.

Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.

Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

5.2 The Oncology Sales Specialist (Cephalon, Inc. Sales Organization)

Full time Oncology Sales Specialists have been placed in the field to personally call on the target audience. The Oncology Sales Specialists are the primary day to day link to the physicians, nurses and pharmacists who will be using the product. The Oncology Sales Specialists play a key role in implementing the RMP.

Each Oncology Sales Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by one week of in-house training at Cephalon, Inc. corporate headquarters and at least by one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and Cephalon, Inc. expectations regarding sales activity in the field. Importantly, Oncology Sales Specialists are tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the Oncology Specialists personally called on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they educated the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies were called on by Oncology Specialists in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group were offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These programs provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will

be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of *Actiq* to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. This letter will be slightly revised from the currently approved one to reflect Cephalon's practices. It will be reviewed by FDA for prior approval before issue. Moreover, the compensation program for Oncology Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the Oncology Sales Specialist will discuss a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD-ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use. Revisions to these materials to reflect the new packaging will also be submitted to FDA prior to use.

5.3 Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

5.4 Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

5.4.1 *Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including:

- *Actiq* Package Insert and *Actiq* Patient Leaflet

- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD-ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

5.4.2 The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* internet site for more information. The letter must have FDA review and prior approval before issue.

5.4.3 The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

5.4.4 Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5 Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5.1 *Actiq* CD-ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in Attachment 7. This program will be available via mass direct mail, the Oncololgy Specialist and the *Actiq* internet site.

5.5.2 *Actiq* Internet Site

An *Actiq* internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

5.5.3 Emergency 911

This number will be prominently featured in all patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the person (eg, a child) is not awake and alert or is breathing slowly.

5.5.4 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the person (eg, a child) is awake and alert.

6.0 Patient and Caregiver Education

6.1 The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Attachment 8).

- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (Attachment 9).
- Child-Resistant Temporary Storage Container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (Attachment 10). Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.
- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet. Target pharmacists will be given an *Actiq* Welcome Kit by an Oncology Sales Specialist and briefed on how patients can obtain them.

Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet --will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.

6.2 Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages
- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the Oncology Sales Specialist or 1-800 number. This video will be available in either English or Spanish.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

6.3 Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

6.4 Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed., to be read and to be understood by younger children will be distributed. This book has been developed at a 2nd to 4th grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

7.0 Point of Dispensing Interventions

The following activities will be implemented at the *Actiq* points of dispensing. Product samples will not be made available.

7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, vendors of major commercial pharmacy precaution software will be asked to place *Actiq* warnings in their systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.

Examples of pharmacy warning screens and electronically produced patient information sheets are provided as Attachment 11.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an Oncology Sales Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the Cephalon, Inc. Oncology Sales Specialists and be made available to any pharmacist upon request. The package (eg, back panel of shelf carton) and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (eg, the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.

7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.

8.0 Surveillance Goals And Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, Cephalon, Inc. will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1 Direct Patient Feedback

8.1.1 Chain Pharmacy Call Back System

A call back system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include RiteAid, Eckerd, Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, RiteAid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

8.2 Prescription Monitoring

8.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of these data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. These data provide the prescriber's name, the physician specialty and zip code. These data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). Cephalon, Inc. will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

8.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached (see Attachment 12). These data will be reported to the FDA on a quarterly basis as described in section 10.0.

8.2.3 Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

Cephalon, Inc. will receive information on retail pharmacy sales. This information will be shared with the Oncology Sales Specialist. The Oncology Sales Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months a Cephalon, Inc. Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will request information on any additional pharmacies which need to be added to the list. Information from the Cephalon's meetings with wholesalers will be shared with the Oncology Sales Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

8.3 Adverse Events

8.3.1 Cephalon, Inc. Standard Operating Procedure

Cephalon, Inc. has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.

A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated.

Any adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by Cephalon, Inc.. The details of this procedure are summarized below.

a) The incident report is reviewed by an investigation team, and an investigation is initiated. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.

b) The medical experience analyst assigned contacts the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.

c) The medical investigation conclusions are discussed with Cephalon, Inc. to determine reportability.

8.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of diversion (ie, use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of "off label use" (ie, that is used outside of the approved indication for *Actiq*) whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert report ," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (eg, call-in, literature, poison control centers, etc).

8.3.3 Literature Monitoring

In addition to specific event reporting, Cephalon, Inc. maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

8.4.1 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. These data are available once yearly and will be included in the analysis for FDA quarterly reports.

8.5 Abuse

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

8.5.1 Routine Cephalon Interaction with DEA

Cephalon, Inc. will maintain communications with DEA and state drug control authorities.

8.5.2 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

8.5.3 State Drug Control Authorities or State Boards of Pharmacy

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

8.6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that Oncology Sales Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the Oncology Sales Specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted, focused launch/promotional plan.

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1) A letter from Cephalon, Inc.'s Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA review and approval before it is issued.

2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an Oncology Sales Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly *Actiq* prescriptions, Cephalon, Inc. will contact the appropriate professional society (ie, American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total *Actiq* prescriptions for two additional quarters, an aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

9.2 Accidental Ingestion

In the event of an unintended pediatric exposure, Cephalon, Inc. will initiate their standard operating procedure for adverse events detailed in section 8.3.1 of this RMP.

10.0 FDA Reporting

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day Alert reports (see Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these 15–day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

Cephalon, Inc. will provide a quarterly report to the FDA compiled from all data collected by the methods described under the *Actiq* Surveillance and Monitoring Program and Interventions (see Sections 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. Cephalon, Inc. will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the *Actiq* Risk Management Plan. This report will be provided as part of the *Actiq* quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

List of Attachments

1 *Actiq* Dosage Unit (example: 200 mcg)

2 Labeling – Blister Package (example: 200 mcg)

3 Labeling - Shelf Carton (example: 200 mcg)

4 *Actiq* Patient Leaflet

5 *Actiq* Package Insert

6 Elements of RMP to be Included in Speaker Bureau Training

7 *Actiq* CD-ROM Schematic

8 Child Safety Lock

9 Secure Personal Container (ie, "fanny pack")

10 Child-resistant Temporary Storage Container

11 Pharmacy Computer Warning screens

12 IMS National Disease and Therapeutic Index example page

"Red-Lined" Copy of RMP

~~CONFIDENTIAL~~

Actiq®

(oral transmucosal fentanyl citrate)

Risk Management Program

(~~November 4, 1998~~February 9, 1999)

NDA Number: 20-747

Sponsor:

Anesta Corp.
4745 Wiley Post Way
Plaza 6, Suite 650
Salt Lake City, UT 84116
801-~~595-~~.595.1405

Marketing Partner:

Abbott Laboratories
Hospital Products Division
Abbott Park, IL 60064

19- 079

~~FDA Approved Version - 11/4/98~~ebruary 9, 1999

TABLE OF CONTENTS

1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1. accidental ingestion of *Actiq* by children
2. improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3. diversion or abuse

Anesta Corp. and Abbott Laboratories have designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- ~~*Actiq*'s CII status~~CII status for *Actiq*

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portions of this RMP should be used in a promotional context or used to promote *Actiq* in a manner inconsistent with the product label.

The ~~Risk Management Plan~~MP and all of its components ~~will~~should be fully operational at the time of launch.

1.1—_Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children

- *Actiq* could be harmful or fatal to a child if accidentally ingested
- *Actiq* must be properly stored and handled
- *Actiq* must be properly disposed of after use
- Healthcare professionals must counsel patients on child safety messages
- Accessible and easily understood directions on what to do in case of accidental ingestion

- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for use in acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - *Actiq* is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients

- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

2.0 Product Definition

The *Actiq* unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a raspberry-flavored lozenge on a handle (see ~~Figure~~Attachment 1). *Actiq* provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that *Actiq* may be perceived as a lollipop. Because of the design of the *Actiq* unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

2.1 *Actiq* Unit

The *Actiq* unit consists of an opaque, white to off-white drug matrix that has been opacified and colored to make it look less appealing to children. Its handle has been designed with a "paddle" with a molded "Rx" in the center to identify it as a product for medical use. Additionally, on the back side of the paddle the word "fentanyl" is clearly visible.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use). The handle carries

legible, laser-engraved product identification information (ie, microgram content of active drug, product code, ~~manufacturer~~Abbott logo, and "fentanyl") in 9 point, charcoal-gray type on a pure white background. The laser-engraved imprint on the handle is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning.

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~~[Insert figure 1]~~

2.2—*Actiq* Child-Resistant Pouch

- ~~See Figures 2 and 3.~~

Each *Actiq* unit is individually sealed in its own child-resistant pouch. The *Actiq* pouch is made of a heavy, multi-layer laminated foil material and requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a 99% effectiveness rating, exceeding the 80% requirement.

Individual child-resistant packaging (one dosage unit in each pouch) is intended to minimize exposure by limiting access to just one unit at a time.

The pouch is opaque. A child cannot see the unit when it is in its pouch. The pouch does not resemble food or most candy wrappers.

The dosage strength of each unit is marked on each handle, and on the foil pouch and shelf carton. The colors are a secondary aid in product identification.

Gray	200 mcg
Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

The front of each pouch utilizes an icon to draw attention to warnings about child safety and opioid tolerance, standard product identification information is also included on the front of the pouch (see Attachment 2). The back of each pouch contains the same icon, plain-language warnings about child safety and proper product storage, and a reminder to read the *Actiq* Patient Leaflet.

The front of each pouch contains the CII symbol, a "May be habit forming" warning, and an "Rx only" warning.

~~[Insert figure 2--pouch front]~~

~~[Insert figure 3 - pouch back]~~

2.3—*Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (~~Figure 4, 6 pages~~Attachment 3). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.

- The right hand side of the back of the shelf carton contains a designated location for the application of the pharmacy-dispensing label. A checklist for the pharmacist is included in this space. The checklist reminds the pharmacist to make sure the patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet,~~ and~~ to discuss the *Actiq* Welcome Kit, and to counsel the patient about disposal of partially consumed units.

~~Kit.~~

- ~~prominent instructions on what to do in case of an accidental~~On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units,~~ and~~ a reminder to read the *Actiq* Patient Leaflet~~.~~, and ~~Below this space are~~ prominent instructions on what to do in case of an accidental exposure.

- On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet .

At the initiation of *Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200 mcg units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in a similar fashion.

Each shelf carton contains eight strips of three pouches, for a total of 24 pouches of a single strength of *Actiq*. The shelf carton represents approximately a ten day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

~~Insert Figure 4-1~~

~~Insert figure 4-2~~

~~Insert figure 4-3~~

~~Insert figure 4-4~~

~~Insert figure 4-5~~

~~Insert figure 4-6~~

2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf cartons to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for ~~titration and~~ prescribing.

2.4.1 Multiple Dosage Strengths

Actiq will be made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed.*

2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

3.0 Labeling

3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)

- ~~100% drug accountability by individual count is required~~strict accountability of finished units
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to ~~ensure~~check for a legitimate medical purpose before dispensing

~~*Actiq*'s~~The status of *Actiq* as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and ~~three~~four copies will be packaged in every shelf carton (~~RMP~~see Attachment ~~1~~4). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *Actiq* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.
- The *Actiq* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized "walk through" of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call ~~1-800 POISON CONTROL~~Poison Control at 1-800-690-3924 if the patient or child is awake
  - instructions for care of the patient or child who is having trouble breathing or not breathing at all
- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word "must" is used instead of the word "should." The warning

language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid ~~pain medicines. . .~~" ~~is used.~~

- (narcotic) pain medicines..." is

~~3.3 Package Insert —~~ used.

3.3 Package Insert

The *Actiq* Package Insert (PI) ~~[see RMP Attachment 2],~~ clearly and explicitly communicates messages about child safety, proper patient selection, and prevention of diversion and abuse (see ~~RMP~~ Attachment ~~3~~)5). These messages (see Attachment 6) are important elements of the RMP. The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- Indication: *Actiq* is indicated 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.
- Black box warnings, which are:

  PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

  ***Actiq* is indicated 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.** Patients considered opioid tolerant are those who are taking at least 60 ~~60~~ mg morphine/day, 50 ~~µ~~mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

  Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ***Actiq*** is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

  Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

  Patients and their care-givers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

- Titration instructions which minimize the number of units in the home
- Detailed safe home handling and storage
- Detailed instructions for disposal of used and unused units
- CII designation

4.0 Professional Medical Education

Anesta and Abbott will work in conjunction with FDA (through the Office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to *Actiq*.

4.1—Key Message Points

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages, which have been described earlier in section 1.1 of this RMP, include:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product
- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, will be provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

4.2—Breakthrough Cancer Pain Nursing Medical Education Monograph

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

4.3—The *Actiq* Speakers Bureau / Medical Education Programs

Prior to product launch, Anesta and Abbott will formally train the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment ~~2~~6):

- ~~Approximately~~at least 50 prominent physician educators in pain management
- ~~Approximately~~at least 50 prominent nurse educators in pain management
- ~~Approximately~~at least 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional, and national settings.

4.4—Publications

~~Anesta and Abbott will publish articles, in peer-reviewed journals, messages that will~~Manuscripts will be submitted to peer-reviewed journals for consideration. They will include messages that reinforce elements of this RMP. The ~~publications selected~~manuscripts selected for publication are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

4.4.1—Broad-Based Publications

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (circulation 10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)
- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

4.4.2—Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses, and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. Abbott and Anesta will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, Anesta will contact these publications to request increased emphasis on the RMP elements.

4.4.3—_Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

4.4.4—_Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

4.4.5—_Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)
- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000+)
- Journal of Managed Care Pharmacy (circulation 40,000+)

4.4.6—_Pharmacy Newsletters (Print and Electronic)

Abbott and Anesta will ~~incorporate~~request that the *Actiq* key safety messages and new product reviews be incorporated into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS– 4,000 stores
  - RiteAid 3,000 stores
  - Walgreens 2,200 stores
- State board of pharmacy newsletters

4.5—_Communication with DEA

Information on proper disposal of *Actiq* will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

5.0 *Actiq* Launch Program

Actiq will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.

All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients.

Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.

Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

5.2 ~~The *Actiq*~~ The Oncology Specialist (Abbott Sales Organization)

~~Abbott will place approximately 40 full time *Actiq* Specialists~~pproximately 40 full time Oncology Specialists will be placed in the field to personally call on the target audience. The ~~*Actiq*~~Oncology Specialists will be the primary~~,~~ day to day link to the physicians, nurses and pharmacists who will be using the product. The ~~*Actiq*~~Oncology Specialists will play a key role in implementing the RMP.

Each ~~*Actiq*~~Oncology Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with four home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by two weeks of in-house training at Abbott corporate headquarters and at least one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and Abbott expectations regarding sales activity in the field. Importantly, ~~*Actiq*~~Oncology Specialists will be tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the ~~*Actiq*~~Oncology Specialists will personally call on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they will educate the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies will be called on by the ~~*Actiq*~~Oncology Specialist in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group will be offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These programs will ~~all~~ provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of *Actiq* to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. The letter must have FDA review and prior approval before issue.

Moreover, the compensation program for ~~*Actiq*~~Oncology Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the ~~*Actiq*~~Oncology Specialist will ~~demonstrate~~iscuss a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD-ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use.

5.3—_Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

5.4—_Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

5.4.1—_*Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including:

- *Actiq* Package Insert and *Actiq* Patient Leaflet
- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD-ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

5.4.2—The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* internet site for more information. The letter must have FDA review and prior approval before issue.

5.4.3—The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

5.4.4—Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5—Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5.1—*Actiq* CD-ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in ~~RMP~~ Attachment 47. This program will be available via mass direct mail, the ~~*Actiq*~~Oncololgy Specialist and the *Actiq* internet site.

5.5.2—*Actiq* Internet Site

An *Actiq* internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

5.5.3—Emergency 911

This number will be prominently featured in all patient education ~~and promotional~~ materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the p~~atient or child~~erson (eg, a child) is not awake and alert or is breathing slowly.

5.5.4—Central 1-800 Poison Control Number

A single 1-800 telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in ~~all patient education and promo~~patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the p~~atient~~erson (eg, a child) is awake and alert.

6.0 Patient and Caregiver Education

6.1—The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a ~~magnetic~~ lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (~~Figure 5~~Attachment 8).
- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (~~Figure 6~~Attachment 9).
- Child-Resistant Temporary Storage Container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (~~Figure 7~~Attachment 10). Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.
- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet. Target pharmacists will be given an *Actiq* Welcome Kit by an ~~*Actiq*~~Oncology Specialist and briefed on how patients can obtain them.

Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet -- will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.

~~Insert Figure 5 - child safety lock~~

~~Insert Figure 6- fanny pack~~

~~Insert Figure 7- child resistant storage container~~

6.2—_Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages
- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the ~~*Actiq*~~Oncology Specialist or 1-800 number. This video will be available in either English or Spanish.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

6.3—_Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

6.4—_Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed., to be read and to be understood by younger children will be distributed. This book has been developed at a 2nd to ~~3rd~~4th grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

7.0 Point Of Dispensing Interventions

The following activities will be implemented at the *Actiq* points of dispensing. Product samples will not be made available.

7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, ~~*Actiq* warnings will be placed in the~~vendors of major commercial pharmacy precaution software will be asked to place *Actiq* warnings in their systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.

Examples of pharmac~~isty~~ warning screens and electronically produced patient information sheets are provided as Attachment ~~5~~11.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an ~~*Actiq*~~Oncology Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the Abbott ~~*Actiq*~~Oncology Specialists and be made available to any pharmacist upon request. The package (eg, back panel of shelf carton) and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (~~e.g.~~g, the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.

7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.

8.0 Surveillance Goals And Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, Abbott/Anesta will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1—_Direct Patient Feedback

8.1.1—_Chain Pharmacy Call Back System

A call back system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include RiteAid, Eckerd, Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, RiteAid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

8.2—_Prescription Monitoring

8.2.1—_IMS Xponent

Prescription data will be routinely monitored. The source of this data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. Thi~~s data provide~~se~~se~~ data provide the prescriber's name, the physician specialty and zip code. Thi~~s~~se data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). Abbott will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

8.2.2—IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached ~~as RMP~~(see Attachment ~~6~~12). These data will be reported to the FDA on a quarterly basis as described in section 10.0.

8.2.3—Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

~~Through its chargeback system,~~Abbott will receive information on retail pharmacy sales ~~from drug wholesalers~~. This information will be shared with the ~~*Actiq*~~Oncology Specialist. The ~~*Actiq*~~Oncology Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months an Abbott Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will ~~reinforce appropriate product usage and confirm the accuracy of the high volume *Actiq* pharmacy listing on which the *Actiq* Specialists are visiting~~quest information on any additional pharmacies which need to be added to the list. Information from the Abbott Trade Specialists' meetings with wholesalers will be shared with the ~~*Actiq*~~Oncology Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

8.3—Adverse Events

8.3.1—Abbott Standard Operating Procedure

Abbott has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.

A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated.

~~All serious events~~ny adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by Abbott. The details of this procedure are summarized below.

a) The incident report is reviewed by ~~the *Actiq* Incident Review Team and an action plan is develop~~an investigation team, and an investigation is initiated. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.

b) ~~An investigation team is assigned and contact made with~~The medical experience analyst assigned contacts the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.

~~c) The investigation team report conclusions are reported to the Incident Review Team, which consults with senior management to determine if corrective action should be recommended and/or taken.~~

c) ~~A schematic of the Incident Review Team and process is attached as RMP Attachment 7~~medical investigation conclusions are discussed with Anesta to determine reportability.

8.3.2—Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of diversion (~~i.e.~~e, use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of "off label use" (~~i.e.~~e, that is used outside of the approved indication for *Actiq*) whether or not the experience~~s~~ is unexpected, will be processed and reported to the FDA as a "15 day Alert."

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert report ," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (~~e.g.~~g, call-in, literature, poison control centers, etc).

8.3.3—Literature Monitoring

In addition to specific event reporting, Abbott maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4—Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

8.4.1—Central 1-800 Poison Control Number

A single 1-800 telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be

highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4.2 ~~Toxic Exposures~~ Toxic Exposure Surveillance System (TESS)

T~~ESS~~oxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. Th~~is~~ese data ~~is~~are available once yearly and will be included in the analysis for FDA quarterly reports.

8.5 Abuse

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

8.5.1 Routine Abbott Interaction with DEA

Abbott Laboratories Corporate Regulatory Affairs maintains a proactive program to identify possible product diversion. Abbott routinely visits DEA District offices with jurisdiction over Abbott distribution facilities to review information on the potential "street use" of Abbott products. In addition, an interactive relationship has been developed so that Abbott is alerted to specific instances. A~~ny incident is investigated and resolved in conjunction with the~~bbott will cooperate with DEA and state drug control authorities' investigations, as requested.

8.5.2 Abbott Exceptions System

Actiq will be added to Abbott's exception reporting system to the DEA. Under this system, any orders that exceed the norm by two or more standard deviations are reported to the DEA for follow-up and investigation.

8.5.3 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

8.5.4 State Drug Control Authorities or State Boards of Pharmacy

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

8.6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that ~~*Actiq*~~Oncology Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the ~~*Actiq* s~~Oncology Specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted, focused launch/promotional plan.

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1) A letter from Abbott's Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA revisionsew and approval before it is issued.

2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an ~~*Actiq*~~Oncology Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly *Actiq* prescriptions, Abbott will contact the appropriate professional society (~~i.e.~~e, American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total *Actiq* prescriptions for ~~2~~two additional quarters, an aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

9.2 Accidental Ingestion

In the event of ~~a serious child poisoning report~~n unintended pediatric exposure, Abbott will initiate their standard operating procedure for adverse events detailed in section 8.3.1 of this RMP ~~and in RMP Attachment 7.~~.

10.0 FDA Reporting

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day ~~"Alert Reports"~~Alert reports (see Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these ~~"15-day Alert reports" will be sent to Surveillance and Monitoring (OPDRA~~15-day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

Anesta/Abbott will provide a quarterly report to the FDA compiled from all data collected by the methods described under the *Actiq* Surveillance and Monitoring Program and Interventions (see Sections 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. Anesta/Abbott will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the *Actiq* Risk Management Plan. This report will be provided as part of the *Actiq* quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

List of Attachments

1 *Actiq* ~~Patient Leaflet~~

~~2 *Actiq* Package Insert~~

~~3 Elements of RMP to be included in Speaker Bureau Training~~

~~4 *Actiq* CD-ROM schematic~~

~~5~~Dosage Unit (example: 200 mcg)

2 Labeling - Foil Pouch (example: 400 mcg)

3 Labeling - Shelf Carton (example: 400 mcg)

4 *Actiq* Patient Leaflet

5 *Actiq* Package Insert

6 Elements of RMP to be Included in Speaker Bureau Training

7 *Actiq* CD-ROM Schematic

8 Child Safety Lock

9 Secure Personal Container (ie, "fanny pack")

10 Child-resistant Temporary Storage Container

11 Pharmacy Computer Warning screens

~~6~~12 IMS National Disease and Therapeutic Index example page

~~7 Incident Team schematic~~

Actiq®

(oral transmucosal fentanyl citrate)

Risk Management Program

~~(February 91, 1999)~~~~July 20~~August 1, 2001

NDA Number: 20-747

Sponsor:

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a Subsidiary of
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TABLE OF CONTENTS

1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1. accidental ingestion of *Actiq* by children
2. improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3. diversion or abuse

~~Anesta Corp. and Abbott Laboratories~~ Anesta Corporation, a ~~s~~Subsidiary of Cephalon, Inc. ~~have~~ hass designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- CII status for *Actiq*

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portions of this RMP should be used in a promotional context or used to promote *Actiq* in a manner inconsistent with the product label.

The RMP and all of its components should be fully operational at the time of launch.

1.1 Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children
  - *Actiq* could be harmful or fatal to a child if accidentally ingested
  - *Actiq* must be properly stored and handled
  - *Actiq* must be properly disposed of after use
  - Healthcare professionals must counsel patients on child safety messages
  - Accessible and easily understood directions on what to do in case of accidental ingestion
- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for use in acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - *Actiq* is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients
- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

2.0 Product Definition

The *Actiq* unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a ~~rasp~~berry-flavored lozenge on a handle (see Attachment 1). *Actiq* provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that *Actiq* may be perceived as a lollipop. Because of the design of the *Actiq* unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

2.1 *Actiq* Unit

The *Actiq* unit consists of an opaque, white to off-white solid drug matrix that appears medicinal ~~has been opacified and colored~~ to make it look less appealing to children. ~~Its handle has been designed with a "paddle" with a molded "Rx" in the center to identify it as a product for medical use. Additionally, on the back side of the paddle the word "fentanyl" is clearly visible.~~ The solid drug matrix and the tag at the end of the handle ~~will~~ indicate the dosage strength. The handle tag is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning. A yellow triangle icon is also imprinted on the handle tag as a reminder of the child safety precautions.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use). ~~The handle carries legible, laser-engraved product identification information (ie, microgram content of active drug, product code, Abbott logo, and "fentanyl") in 9 point, charcoal-gray type on a pure white background. The laser-engraved imprint on the handle is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning.~~

2.2 *Actiq* Child-Resistant ~~Blister Pouch~~Package

Each *Actiq* unit is individually sealed in its own child-resistant ~~pouch~~blister package. ~~The *Actiq* pouch is made of a heavy, multi-layer laminated foil material and~~ This blister package is made of thick PVC/A~~-a~~clar blister packaging material with a strongly sealed foil-/paper lidding that requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a ~~99~~100% effectiveness rating, exceeding the 80% requirement.

Individual child-resistant packaging (one dosage unit in each ~~pouch~~blister package) is intended to minimize exposure by limiting access to just one unit at a time.

The ~~pouch~~ blister package is opaque~~.~~ so that ~~A~~ a child cannot see the unit when it is in ~~its~~ the ~~pouch~~blister package. The ~~pouch~~ blister package does not resemble food or ~~most~~ candy wrappers.

The dosage strength of each unit is marked on the solid drug matrix, on each handle tag, on the blister package and on the ~~foil pouch and~~ shelf carton. The handle tags, blister packages and cartons have colored markings ~~that~~ that ~~The colors~~ are a secondary aid in product identification.

Gray	200 mcg
Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

The ~~front of each pouch~~ blister package utilizes an icon to draw attention to warnings about child safety and opioid tolerance~~;~~ and standard product identification information, ~~is also included on the front of the pouch~~ (see Attachment 2). ~~The back of each pouch contains the same icon, plain language warnings about child safety and proper product storage, and a~~ It also contains a reminder to read the *Actiq* Patient Leaflet.

In addition the blister package label ~~The front of each pouch~~ contains the CII symbol, a "May be habit forming" warning, and an "Rx only" warning.

2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Attachment 3). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.

- The ~~right hand side of the~~ back of the shelf carton contains ~~a designated location for the application of the pharmacy dispensing label. A~~ a checklist for the pharmacist, ~~is included in this space.~~ The checklist reminds the pharmacist to make sure the patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet, to discuss the *Actiq* Welcome Kit, and to counsel the patient about disposal of partially consumed units.

- On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units, a reminder to read the *Actiq* Patient Leaflet, and prominent instructions on what to do in case of an accidental exposure.

- On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet .

At the initiation of *Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200 mcg units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in a similar fashion.

Each shelf carton contains ~~eight~~ ten strips of three ~~pouches~~blister packages, for a total of ~~24 pouches~~30 blister packages of a single strength of *Actiq*. Each carton will also include five patient leaflets and one package insert. The shelf carton represents approximately a ten day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf cartons to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for prescribing.

2.4.1 Multiple Dosage Strengths

Actiq ~~will be~~ is made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed.*

2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

3.0 Labeling

3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)
- strict accountability of finished units
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to check for a legitimate medical purpose before dispensing

The status of *Actiq* as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and ~~four~~ five copies will be packaged in every shelf carton (see Attachment 4). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *Actiq* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.
- The *Actiq* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized "walk through" of ~~-~~disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call Poison Control ~~(~~at 1-800-690-3924 ~~number is provided)~~ if the patient or child is awake
  - instructions for care of the patient or child who is having trouble breathing or not breathing at all
- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word "must" is used instead of the word "should." The warning language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines..." is used.

3.3 Package Insert

The *Actiq* Package Insert (PI) clearly and explicitly communicates messages about child safety, proper patient selection, and prevention of diversion and abuse (see Attachment 5). These messages (see Attachment 6) are important elements of the RMP. The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- Indication: *Actiq* is indicated 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.
- Black box warnings, which are:

  PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

  ***Actiq* is indicated 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.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

  Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ***Actiq*** is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

  Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

  Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

- Titration instructions which minimize the number of units in the home
- Detailed safe home handling and storage
- Detailed instructions for disposal of used and unused units
- CII designation

The *Actiq* insert will be included in each shelf carton.

4.0 Professional Medical Education

~~Anesta and Abbott~~ Cephalon, Inc. will work in conjunction with FDA (through the Office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to *Actiq*.

4.1 Key Message Points

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages, which have been described earlier in section 1.1 of this RMP, include:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product
- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, ~~will be~~ are provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

4.2 Breakthrough Cancer Pain Nursing Medical Education Monograph

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

4.3 The *Actiq* Speakers Bureau / Medical Education Programs

Prior to product launch, Anesta and Abbott ~~will~~ formally trained the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment 6):

- At least 50 prominent physician educators in pain management
- At least 50 prominent nurse educators in pain management
- At least 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional, and national settings.

4.4 Publications

Manuscripts will be submitted to peer-reviewed journals for consideration. They will include messages that reinforce elements of this RMP. The manuscripts selected for publication are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

4.4.1 Broad-Based Publications

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (circulation 10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)
- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

4.4.2 Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses, and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. ~~Abbott and Anesta~~ Cephalon, Inc. will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, ~~Anesta~~Cephalon, Inc. will contact these publications to request increased emphasis on the RMP elements.

4.4.3 Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

4.4.4 Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

4.4.5 Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)
- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000+)
- Journal of Managed Care Pharmacy (circulation 40,000+)

4.4.6 Pharmacy Newsletters (Print and Electronic)

~~Abbott and Anesta Cephalon, Inc.~~ During the initial launch of Actiq, requests were made~~will request~~ that the *Actiq* key safety messages and new product reviews were to be~~are~~ incorporated into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS 4,000 stores
  - RiteAid 3,000 stores
  - Walgreens 2,200 stores

- State board of pharmacy newsletters

4.5 Communication with DEA

Information on proper disposal of *Actiq* will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

5.0 *Actiq* Launch Program

Actiq will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.

All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients.

Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.

Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

5.2 The ~~Oncology Specialist~~Oncology Sales Specialist (~~Abbott~~Cephalon, Inc. Sales Organization)

~~Approximately 40 f~~Full time Oncology Sales Specialists ~~will have been~~be placed in the field to personally call on the target audience. The Oncology Sales Specialists ~~will be~~are the primary day to day link to the physicians, nurses and pharmacists who will be using the product. The Oncology Sales Specialists ~~will~~ play a key role in implementing the RMP.

Each Oncology Sales Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with ~~four~~ home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by one~~two~~ week~~s~~ of in-house training at ~~Abbott~~Cephalon, Inc. corporate headquarters and at least by one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and ~~Abbott~~Cephalon, Inc. expectations regarding sales activity in the field. Importantly, ~~Oncology Specialist~~Oncology Sales Specialists ~~will be~~ are tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the Oncology ~~Sales~~ Specialists ~~will~~ personally called on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they ~~will~~ educated the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies were~~ill be~~ called on by ~~the~~ Oncology Specialists in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group ~~will be~~were offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These

programs ~~will~~ provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of *Actiq* to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. The ~~is~~ letter will be slightly revised from the currently approved one to reflect Cephalon's practices. It will be reviewed ~~must have~~by FDA for ~~review and~~ prior approval before issue. Moreover, the compensation program for Oncology Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the ~~Oncology Specialist~~Oncology Sales Specialist will discuss a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD-ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use. Revisions to these materials to reflect the new packaging will also be submitted to FDA prior to use.

5.3 Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

5.4 Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

5.4.1 *Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including:

- *Actiq* Package Insert and *Actiq* Patient Leaflet
- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD-ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

5.4.2 The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* internet site for more information. The letter must have FDA review and prior approval before issue.

5.4.3 The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

5.4.4 Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5 Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

5.5.1 *Actiq* CD-ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in Attachment 7. This program will be available via mass direct mail, the Oncololgy Specialist and the *Actiq* internet site.

5.5.2 *Actiq* Internet Site

An *Actiq* internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

5.5.3 Emergency 911

This number will be prominently featured in all patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the person (eg, a child) is not awake and alert or is breathing slowly.

5.5.4 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the person (eg, a child) is awake and alert.

6.0 Patient and Caregiver Education

6.1 The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Attachment 8).
- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (Attachment 9).
- Child-Resistant Temporary Storage Container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (Attachment 10). Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.
- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet. Target pharmacists will be given an *Actiq* Welcome Kit by an ~~Oncology Specialist~~Oncology Sales Specialist and briefed on how patients can obtain them.

Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet --will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.

6.2 Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages

- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the ~~Oncology Specialist~~Oncology Sales Specialist or 1-800 number. This video will be available in either English or Spanish.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

6.3 Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

6.4 Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed., to be read and to be understood by younger children will be distributed. This book has been developed at a 2nd to 4th grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

7.0 Point oOf Dispensing Interventions

The following activities will be implemented at the *Actiq* points of dispensing. Product samples will not be made available.

7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, vendors of major commercial pharmacy precaution software will be asked to place *Actiq* warnings in their systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.

Examples of pharmacy warning screens and electronically produced patient information sheets are provided as Attachment 11.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an ~~Oncology Specialist~~Oncology Sales Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the ~~Abbott~~Cephalon, Inc. ~~Oncology Specialist~~Oncology Sales Specialists and be made available to any pharmacist upon request. The package (eg, back panel of shelf carton) and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (eg, the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.

7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.

8.0 Surveillance Goals And Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered

- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, ~~Abbott/Anesta~~ Cephalon, Inc. will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1 Direct Patient Feedback

8.1.1 Chain Pharmacy Call Back System

A call back system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include RiteAid, Eckerd, Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, RiteAid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

8.2 Prescription Monitoring

8.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of theseis data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. These data provide the prescriber's name, the physician specialty and zip code. These data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). AbbottCephalon, Inc. will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

8.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached (see Attachment 12). These data will be reported to the FDA on a quarterly basis as described in section 10.0.

8.2.3 Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

AbbottCephalon, Inc. will receive information on retail pharmacy sales. This information will be shared with the Oncology Sales Specialist. The Oncology SpecialistOncology Sales Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months an AbbottCephalon, Inc. Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will request information on any additional pharmacies which need to be added to the list. Information from the Abbott Trade Specialists' Cephalon's meetings with wholesalers will be shared with the Oncology Sales Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

8.3 Adverse Events

8.3.1 ~~Abbott~~Cephalon, Inc. Standard Operating Procedure

~~Abbott~~Cephalon, Inc. has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.

A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated.

Any adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by ~~Abbott~~Cephalon, Inc.. The details of this procedure are summarized below.

a) The incident report is reviewed by an investigation team, and an investigation is initiated. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.

b) The medical experience analyst assigned contacts the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.

c) The medical investigation conclusions are discussed with ~~Anesta~~Cephalon, Inc. to determine reportability.

8.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of diversion (ie, use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of "off label use" (ie, that is used outside of the approved indication for *Actiq*) whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert report ," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (eg, call-in, literature, poison control centers, etc).

8.3.3 Literature Monitoring

In addition to specific event reporting, ~~Abbott~~Cephalon, Inc. maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

8.4.1 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

8.4.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. These data are available once yearly and will be included in the analysis for FDA quarterly reports.

8.5 Abuse

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

8.5.1 Routine ~~Abbott~~ Cephalon Interaction with DEA

~~Abbott Laboratories Corporate Regulatory Affairs maintains a proactive program to identify possible product diversion. Abbott routinely visits DEA District offices with~~

~~jurisdiction over Abbott distribution facilities to review information on the potential "street use" of Abbott products. In addition, an interactive relationship has been developed so that Abbott is alerted to specific instances. Abbott~~Cephalon, Inc. will ~~cooperate~~ maintain communications with DEA and state drug control authorities~~, investigations, as requested.~~

~~8.5.2 Abbott Exceptions System~~

~~*Actiq* will be added to Abbott's exception reporting system to the DEA. Under this system, any orders that exceed the norm by two or more standard deviations are reported to the DEA for follow-up and investigation.~~

8.5.~~2~~3 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

8.5.~~3~~4 State Drug Control Authorities or State Boards of Pharmacy

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

8.~~6~~6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that ~~Oncology Specialist~~Oncology Sales Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the ~~Oncology Specialist~~Oncology Sales Specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted, focused launch/promotional plan.

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1) A letter from ~~Abbott~~Cephalon, Inc.'s Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA review and approval before it is issued.

2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an ~~Oncology Specialist~~Oncology Sales Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly *Actiq* prescriptions, ~~Abbott~~Cephalon, Inc. will contact the appropriate professional society (ie, American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total *Actiq* prescriptions for two additional quarters, an

aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

9.2 Accidental Ingestion

In the event of an unintended pediatric exposure, ~~Abbott~~Cephalon, Inc. will initiate their standard operating procedure for adverse events detailed in section 8.3.1 of this RMP.

10.0 FDA Reporting

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day Alert reports (see Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these 15–day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

~~Anesta/Abbott~~Cephalon, Inc. will provide a quarterly report to the FDA compiled from all data collected by the methods described under the *Actiq* Surveillance and Monitoring Program and Interventions (see Sections 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. ~~Anesta/Abbott~~ Cephalon, Inc. will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the *Actiq* Risk Management Plan. This report will be provided as part of the *Actiq* quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

List of Attachments

Cephalon

January 16, 2002

Cynthia McCormick, M.D.
Division Head
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
FDA HFD-170; Doc.Cont. Rm. 9B23
5600 Fishers Lane
Rockville, MD 20857

NDA 20-747
Actiq® (Oral Transmucosal Fentanyl Citrate)
Prior Approval Supplement:
Revision to Risk Management Program

Dear Dr. McCormick:

Reference is made to Section 5.2 (The Oncology Specialist) of the Risk Management Program (RMP) document that refers to a letter that the company sends to the Sales Specialist that outlines the Specialists' responsibilities as they relate to the RMP. The only approved letter was that associated with the February 9, 1999 filing of the RMP (S-003). Subsequent to that supplement, a revised letter was submitted in association with the revised RMP dated May 31, 2000 in supplement S-007. On October 16th, 2001, Cephalon received a letter from the Agency that contained comments associated with Section 5.2 of the RMP (submitted in S-007) and a response was submitted on October 26, 2001. There has been no further correspondence from the Agency regarding this supplement but we have readdressed this concern in this supplement (see below) since the Agency's concern, the name of the sales force, is reflected in our proposed letter.

In this supplement, Cephalon is providing a revised letter to be sent to the sales force in order to reflect Cephalon, Inc.'s sales and marketing responsibilities for Actiq, as acknowledged in the November 30, 2000 letter to NDA 20-747 that discussed the transfer of responsibilities from Anesta. For ease of review, we are providing a "red-lined" version using the approved letter from the Feb. 9, 1999 submission showing the proposed revisions. In addition, a letter that incorporates the proposed text is also provided so that

Cephalon, Inc. • 145 Brandywine Parkway • West Chester, PA 19380-4245 • (610) 344-0200 • Fax (610) 344-0065

the reviewer can see the final formatted version. The changes reflect the Cephalon name along with textual edits that reinforce Cephalon's commitment to the RMP principles. In addition, a paragraph was removed to eliminate redundant information. Please note that comments from the Agency (see FDA letter dated October 16, 2001) regarding the name of the sales force has been received. In this regard, please refer to the Cephalon response letter dated October 26, 2001 that states:

> *The Cephalon sales force has been reorganized to accommodate sales in the broader pain area since this sector of the force will support not only Actiq but also products that will be acquired in pending acquisitions. It is our intention, therefore, to name the individuals in this sector of the sales force "Pain Care Specialists" which can be applicable to more than the sales of Actiq.*
>
> *We acknowledge your concern regarding the implication of off-label use; however, the title of the sales force is a business organizational decision that has been established based upon company goals. The title of the sales representative does not impact how the sales force is instructed to sell the product or any other aspect of the implementation of the Risk Management Program which safeguards the sales of Actiq from off-label use.*

We acknowledge that all changes to the RMP require prior approval. Due to obvious business concerns associated with the acquisition of the product, a letter reflecting the Cephalon name needs to be implemented as soon as possible; therefore, we are requesting an expedited review.

If you have any questions regarding this supplement, please contact me by phone at (610) 738-6237 or by fax at (610) 738-6642.

Sincerely,

Carol S. Marchione

Carol S. Marchione
Senior Director,
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No 0910-0338
Expiration Date March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Anesta Corp.	1/16/02
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
610-344-0200	610-738-6642
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: c/o Cephalon, Inc. 145 Brandywine Parkway West Chester, PA 19380-4245	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-747

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
oral tansmucosal fentanyl citrate, OTFC	Actiq

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
1-phenethyl-4-piperidyl propionanilide citrate	

DOSAGE FORM.	STRENGTHS:	ROUTE OF ADMINISTRATION
solid, cooked matrix	200, 400, 600, 800, 1200, 1600 ug	oral transmucosal

(PROPOSED) INDICATION(S) FOR USE:
Actiq is indicated for the management of breakthrough cancer pain, in patients with malignancies who are already receiving and who are tolerant to opioid therapy

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314 94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION. _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION Revision to RMP-related document

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

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

Information previously submitted -- available upon request

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

DMF 5038	Fentanyl Citrate	Johnson Matthey, Inc.
DMF 8906	Artificial Raspberry Flavor #906.014/WC	Flavors of North America, Inc
DMF 1218	Plant Master File	Abbott Laboratories, North Chicago, IL
IND 27,428	Oral Tansmucosal Fentanyl (OTFC)	
NDA 20-195	Fentanyl Oralet (Oral Transmucosal Fentanyl Citrate) 100, 200, 300, 400 ug fentanyl base	

This application contains the following items: *(Check all that apply)*	
	1 Index
	2 Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3 Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g , 21 CFR 314.50(d)(1); 21 CFR 601 2)
	B Samples (21 CFR 314.50 (e)(1); 21 CFR 601 2 (a)) (Submit only upon FDA's request)
	C Methods validation package (e.g , 21 CFR 314.50(e)(2)(i); 21 CFR 601 2)
	5. Nonclinical pharmacology and toxicology section (e g., 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6 Human pharmacokinetics and bioavailability section (e.g , 21 CFR 314 50(d)(3), 21 CFR 601 2)
	7 Clinical Microbiology (e.g , 21 CFR 314 50(d)(4))
	8 Clinical data section (e.g , 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g , 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g , 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations Parts 606, and/or 820
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12
6. Regulations on Reports in 21 CFR 314 80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate

Warning: a willfully false statement is a criminal offense, U S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Kenneth L White	Kenneth L. White, Pharm.D. Vice President, Regulatory Affairs	1/16/02

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
145 Brandywine Parkway West Chester, PA 19380-4245	(610) 344-0200

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

Sales Force Letter Showing Proposed Revisions from FDA-Approved Letter of March, 1999

To: ~~Abbott Laboratories H.P.D. Sales Representatives~~
Pain Care Specialists
Pain Care Area Managers
Medical Liaisons
National Account Managers

RE: Promotion of ~~Actiq~~CTIQ® ~~CII~~ (oral transmucosal fentanyl citrate) C-II

~~Cc: Field Sales Management~~

We are all very excited about the success ACTIQ ~~launch of Actiq® CII (oral transmucosal fentanyl citrate)~~is having in the market place. This product serves an important clinical need in its intended patient population, ~~:::::~~the cancer pain patient with breakthrough pain, and we are proud to be promoting its proper use~~bring the product to market~~.

It is important~~, however,~~ that we remember our responsibility to promote this unique product ~~drug delivery system only for its intended use and patient population. *Actiq* is indicated~~ 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. Promotion of ~~*Actiq*~~ ACTIQ for other indications or patient populations is clearly a violation of ~~Abbott~~ Cephalon's policy and therefore makes violators subject to disciplinary action ~~including termination. As with all drugs, we have an ethical responsibility to assure access to our product by the appropriate patient population in need. In a~~Additionally, ~~you must assure that you provide the prescribing~~ while discussing ACTIQ with clinicians, you must provide ~~with~~ a balanced representation of the Risk Management Program ~~facts~~ regarding ~~its~~ the indications, patient selection, ~~contraindications,~~ side effects, use, ~~and~~ safe handling, child safety, disposal, prevention of diversion and abuse.

~~As we discussed during our training sessions, an appropriately balanced representation of *Actiq* will include the important safety messages, which underlie the Risk Management Program. Note: See attachment for a summary of the Key Safety Messages. It is your responsibility to assure that your customers understand the potential risks, which could come to unintended populations. These include all parameters of keeping *Actiq* out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Use the patient leaflet to educate your customers on proper patient selection, proper disposal and handling of *Actiq*, emergency information, and other important directions.~~

Even though your targeted physician population consists of ~~O~~oncologists and ~~P~~pain management ~~S~~specialists, it is inevitable that you will be contacted by or become aware of other physicians who wish to use ACTIQ~~*Actiq*~~ outside of indication. It is your responsibility to assure that these physicians are instructed on the appropriate use of ACTIQ~~*Actiq*~~ and the potential dangers associated with its use outside ~~its~~ the intended patient population. Again, t~~T~~his instruction should cover ~~include~~ proper use, storage, handling, and disposal requirements in the home as well as indications, contraindications, and side effects.

~~Actiq~~ ACTIQ offers a substantial improvement in the treatment of patients suffering daily from episodes of breakthrough cancer pain which are uncontrolled by their current opioid therapy. We are confident that you will be successful in aiding your clinicians in satisfying this critical unmet need.

~~Regards~~Sincerely,

~~Abbott Laboratories~~Roy Craig
Vice President, Sales

~~Attachment~~

~~ATTACHMENT~~
cc: Mike Wetherholt
Mike Thiem
Chuck DeWildt

Proposed Sales Force Letter

To:

Pain Care Specialists
Pain Care Area Managers
Medical Liaisons
National Account Managers

RE: Promotion of ACTIQ® (oral transmucosal fentanyl citrate) C-II

We are all very excited about the success ACTIQ is having in the market place. This product serves an important clinical need in its intended patient population, the cancer pain patient with breakthrough pain, and we are proud to be promoting its proper use.

It is important that we remember our responsibility to promote this unique product 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. Promotion of ACTIQ for other indications or patient populations is clearly a violation of Cephalon's policy and therefore makes violators subject to disciplinary action. Additionally, while discussing ACTIQ with clinicians, you must provide a balanced representation of the Risk Management Program regarding the indication, patient selection, side effects, use, safe handling, child safety, disposal, prevention of diversion and abuse.

Even though your targeted physician population consists of oncologists and pain management specialists, it is inevitable that you will be contacted by or become aware of other physicians who wish to use ACTIQ outside of indication. It is your responsibility to assure that these physicians are instructed on the appropriate use of ACTIQ and the potential dangers associated with its use outside the intended patient population. Again, this instruction should cover proper use, storage, handling, and disposal requirements in the home as well as indications, contraindications, and side effects.

ACTIQ offers a substantial improvement in the treatment of patients suffering daily from episodes of breakthrough cancer pain which are uncontrolled by their current opioid therapy. We are confident that you will be successful in aiding your clinicians in satisfying this critical unmet need.

Sincerely,

Roy Craig
Vice President, Sales

cc: Mike Wetherholt
Mike Thiem
Chuck DeWildt