MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 17, 2006

To: Bob Rappaport, M.D., Director
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Subject: Consultation NDA 21-947 for Fentanyl Effervescent Buccal Tablets (100, 200, 400, 600, 800 mcg). Review the proposed RMP and other NDA materials related to the abuse potential.
Date of Submission: August 31, 2005
Sponsor: Cephalon, Inc.)

This memorandum responds to a consultation from the Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170, concerning the risks of Fentanyl Effervescent Buccal Tablets (NDA 21-947, Cephalon) as well as a review of the Sponsor's proposed Risk Management Plan (RMP). CSS has reviewed the pertinent sections of the NDA including clinical pharmacology and safety, chemistry, product formulation, clinical trial databases, and the proposed RMP.

I. EXECUTIVE SUMMARY[1]

The fentanyl effervescent buccal tablet product (FEBT) is a highly concentrated, high-dose, highly bioavailable, rapid onset formulation of one of the most potent mu opioid agonists. Fentanyl is estimated to be eighty times as potent as morphine as an analgesic (Reisine and Pasternak in Goodman & Gilman).[2] NDA 21-947 proposes five tablet strengths (100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg) for buccal mucosal administration all indicated for "the management of breakthrough pain in patients with

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[1] This section of the consultation was previously submitted to the NDA file as a separate document on May 9, 2006. CSS, Executive Summary. Silvia N. Calderon, Ph.D. and Deborah B. Leiderman, M.D. Controlled Substance Staff. DFS, NDA #21-947.

[2] Reisine, T. and Pasternak, G. Opioid Analgesics and Antagonists. In Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, 1996.

cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain."

Fentanyl is controlled in Schedule II of the Controlled Substances Act (CSA) as are similar opiates approved for medical use including hydromorphone, morphine, and oxycodone. Schedule II drugs have the highest potential of abuse and pose a high risk to the public health (21 U.S.C. 812).

The risks of unintentional potentially fatal overdose, as well as of misuse or abuse of fentanyl, and of FEBT in particular, are extremely high, even when compared to risks posed by other fentanyl products such as Actiq (oral transmucosal fentanyl citrate).

Actiq was approved in 1998, under Subpart H regulations; implementation of a Risk Management Plan (RMP) was a condition of approval. The Actiq RMP requires strict quarterly reporting of all spontaneous reports of unintended pediatric exposures, off-label use and possible diversion. Unintentional pediatric exposures to Actiq have been reported, the majority of which involve toddlers exposed to partially used lozenges or to the applicator handle. Ready detection and intervention in these exposures was facilitated by the visible applicator stick. The FEBT formulation, in contrast, lacks Actiq's applicator stick for ready retrieval of the product from a child's mouth and produces very high fentanyl plasma levels when ingested or swallowed.

Pharmacokinetic characteristics of FEBT that increase its risks includes its higher bioavailability relative to Actiq (65% ±20 % vs 47% ± 11%) and highly variable individual Tmax, which is unrelated to tablet strength and ranges from 20 minutes to three hours across all dosage strengths.[3]

This new fentanyl formulation, FEBT, poses additional risks to the intended patient population and to the public health. At particular risk are the vulnerable populations of children, including adolescents, and the elderly. Patients are at risk of accidental overdose due to variable and unpredictable levels of opioid tolerance, medication errors related to multiple FEBT strengths of similar tablet size and color, disease-related or drug induced confusion, concomitant CNS depressant medications, and incomplete medical history that might include drug or alcohol abuse. Any accidental pediatric ingestion is likely to be fatal due to the product's high concentration and high bioavailability. Misuse of the formulation by recreational abusers as well as by patients carries a high risk of lethality.

The risk of fatal overdose due to respiratory depression exists even in active opioid abusers who may be regular users of and tolerant to other less potent opioids. The fact that no crushing or extraction of fentanyl from the dosage form is required to rapidly achieve high fentanyl plasma levels will appeal to abusers and misusers; consequently

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[3] Clinical Pharmacology and Biopharmaceutics Review, Chandra S. Chaurasia, Ph.D. and Suresh Doddapaneni, Ph.D., OCPB Division: Division of Clinical Pharmacology. DFS, NDA#21-947.

- The sponsor's RMP is deficient in the areas of risk assessment and prevention, identification of key messages, educational plans, surveillance methodology, signal detection and interventions.
- The Sponsor's RMP which largely relies on education and signal detection cannot adequately manage the risk of the product

RECOMMENDATIONS

It is not clear that all the measures necessary to support the safe use of this product can be implemented in the outpatient setting.

At a minimum the following measures should be implemented:

- Physician supervised dose- titration for each patient as performed in the clinical trials.
- Prescribing limited to oncologists and pain specialists.
- Mandatory education for prescribers, patients and caregivers
- Use of physician and patient/caregiver agreements.
- Limitations on the quantities of tablets prescribed and dispensed.

Specific recommendations addressing education, surveillance, reporting of events of pediatric exposure, off-label use and diversion, as well as reporting frequency, and intervention are expanded upon in the full CSS consultation.

II. BACKGROUND

- PRODUCT DESCRIPTION

Fentanyl effervescent buccal tablets (FEBT) represent a high concentration, rapid onset and highly bioavailable formulation of one of the most potent mu opioid agonists. Fentanyl is estimated to be eighty times as potent as morphine as an analgesic (Reisine and Pasternak in Goodman & Gilman)[5]. FEBT's proposed indication is for "the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain." Proposed tablet strengths are 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg. These tablets are debossed the first digit of the strength

FEBT is designed to be placed in the cheek for a period sufficient to allow disintegration of the tablet, and rapid transmucosal delivery of fentanyl. The median FEBT Tmax is 40.0 minutes (range 25 --180 minutes). FEBT is approximately twice as bioavailable when compared to another rapid delivery fentanyl formulation, Actiq. FEBT employs the OraVescent® drug delivery technology, which utilizes an effervescent reaction to enhance the rate and extent of fentanyl absorbed through the buccal mucosa. The tablets which makes the tablets sweet to taste.

- FENTANYL PHARMACOLOGY AND RISKS

Fentanyl injectable (Sublimaze) has been used for many years in anesthesia practice typically by the intravenous or epidural routes of administration. The development of fentanyl for use outside of the hospital setting is recent. Fentanyl transdermal patches which provide a sustained release of fentanyl over 72 hours have facilitated the use of fentanyl in the treatment of chronic pain. (Duragesic was approved in August, 1990 and a generic version approved in January, 2005, in strengths of 12, 25, 50, 75 and 100 mcg/hour). Actiq, the first approved fentanyl oral transmucosal product, delivers 200, 400, 600, 800, 1200 and 1600 mcg on an applicator stick for the management of breakthrough malignant pain.

All fentanyl products share the risks associated with the μ opioid pharmacological class. In addition to being a potent analgesic agent, fentanyl is a potent diffuse CNS depressant drug. Dose-related CNS depression resulting in respiratory depression, coma and death are the most serious risks. Potentially life-threatening overdose can occur in a range of clinical settings, including accidental overdose, use in non-opiate tolerant patients, dose errors due to patient confusion, inadequate pain control as well as misuse and abuse.

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[5] Reisine, T. and Pasternak, G. Opioid Analgesics and Antagonists. In Goodman & Gilman's The Pharmacological Basis of Therapeutics. Ninth Edition, 1996

As a potent opiate narcotic drug, fentanyl is controlled in the most stringent schedule of the Controlled Substances Act (CSA) for approved drugs, Schedule II. Schedule II drugs have the highest potential for abuse as well as posing significant public health risks.

On July 15, 2005, the FDA issued a Public Health Advisory containing safety warnings related to use of fentanyl transdermal patches. The Advisory was issued in response to reports of death and other serious side effects from overdoses of fentanyl in patients using fentanyl transdermal patches for pain control. Deaths and overdoses have occurred in patients using both the brand name product Duragesic and the generic product. No restrictions on the use of Duragesic were imposed at the time of approval

Actiq was approved (November 4, 1998) under Subpart H regulations with use restricted to the management of breakthrough pain of malignant origin. Implementation of a Risk Management Plan (RMP) was a condition of approval. The RMP not only restricts use to breakthrough pain associated with cancer, but specifies that Actiq should be used by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Actiq's RMP was designed to prevent accidental pediatric exposure, improper patient selection and to prevent diversion and abuse.

FEBT represents a new formulation of fentanyl that allows rapid transmucosal absorption of drug that results in rapid high plasma levels as described above.

- **PHARMACOKINETICS/ PHARMACODYNAMICS –COMPARISON WITH OTHER FENTANYL PRODUCTS**

FEBT is rapidly absorbed whether administered transmucosally as prescribed or swallowed (deliberately or inadvertently). The differences between transmucosal effervescent fentanyl and Actiq in bioavailability and in the fraction absorbed across the mucosa and the gut resulted in a notably higher early systemic exposure for transmucosal effervescent fentanyl compared with transmucosal Actiq. The plasma levels achieved with FEBT when compared on a microgram for microgram basis, are higher than those achieved with Actiq.

FEBT exhibits rapid dissolution across a wide pH range (1 -7.5). Buccal administration results in rapid delivery and enhanced absorption of fentanyl, as demonstrated by Cmax, Tmax and AUC 0-tmax values, with increased bioavailability (800 mcg FEBT is approximately equivalent to 1600 mcg Actiq).

Buccal administration of ***FEBT*** showed greater bioavailability (F_{OVF}=0.65) than ***Actiq*** (F_{ACTIQ}=0.47) or **swallowed *FEBT*** (F_{ORAL}=0.31). Approximately one-third (F_{ORAL}=0.31) of **swallowed *FEBT*** escaped hepatic first-pass elimination and became systemically available. Fentanyl peak plasma levels of 1.59 ± 0.9 ng/mL were achieved within 40 minutes (mean with Tmax range 25 to 180 minutes after buccal application of a single 800 mcg fentanyl effervescent tablet).

Following initial ***Duragesic*** application, serum fentanyl concentrations increase gradually to reach peak serum concentrations of fentanyl generally within 24 to 72 hours. Serum fentanyl concentrations achieved are proportional to the ***Duragesic*** delivery rate. Following initial application of the ***Duragesic*** [illegible] mcg/hour patch, fentanyl plasma levels of 2.5 ± 1.2 ng/mL are generally reached within 36.8 ±15.7 hours (Duragesic label).

The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (Mosby's Drug Consult™ - 15th Ed. - 2005). Analgesia is associated with fentanyl plasma levels of 0.6 ng/mL. These values are not absolute as there is a large intersubject variability based on characteristics such as opioid tolerance, chronic use and pain status, as well as other poorly understood variables. Plasma levels associated with respiratory depression are similarly affected by these variables.

In opiate-naïve patients, minimum effective analgesic serum fentanyl concentrations range from 0.2-2 ng/mL. Adverse effects of the drug generally increase as serum concentrations exceed 2 ng/mL. While respiratory depression (e.g., hypoventilation) can occur throughout the therapeutic range of fentanyl serum concentrations, the risk increases in a concentration-dependent fashion, particularly above plasma levels of 2 ng/mL in opiate-naive patients. Patients with underlying pulmonary conditions are especially high risk. Diffuse CNS depression is observed at serum fentanyl concentrations above 2- 3 ng/mL in opiate-naive patients. Anesthesia and profound respiratory depression generally occur at concentrations of 10-20 ng/mL. (AHFS DI 2005)

Table 1 compares fentanyl pharmacokinetic parameters after single dose administration of FEBT as a function of route -- buccal, swallowed or intravenous -- administration. Cmax achieved after **swallowing** an ***800 mcg FEBT*** fentanyl effervescent buccal tablet is similar to that observed after ***FEBT 400 mcg*** fentanyl effervescent buccal tablet is used **as indicated**.

Table 1: Fentanyl single-dose pharmacokinetic parameters following administration of fentanyl effervescent buccal tablets. **FEBT** (buccal and swallowed), **Actiq**, and **intravenous fentanyl**.

Treatment Dose (mcg) Route (Study ID)	**Mean ±SD pharmacokinetic parameters of fentanyl**[a]			
	Cmax (ng/mL)	Tmax (minutes)[b]	AUC (0-tmax)	AUC (t-∞) (ng.h/mL)
FEBT 400 Oral **Buccal** (Study 1028)	1.02 (0.42)	46.8 (20.0-240.0)	0.40 (0.18)	6.48 (2.98)
Actiq 800 Oral **Buccal** (Study1028)	1.26 (0.41)	90.8 (35.0-240.1)	0.28 (0.10)	9.58 (3.91)
FEBT 800 Oral **Swallowed** (Study 1028)	0.98 (0.54)	90.1 (40.5-240.0)	0.11 (0.14)	6.60 (4.47)
FEBT 800 Oral **Buccal** (Study1027)	1.59 (0.90)	40.0 (25.0-180.0)	0.52 (0.38)	9.05 (3.72)
Fentanyl 400 **iv Infusion** (1028)	3.00 (1.11)	NA	1.43 (0.39)	10.29 (2.88)

[a]NDA 21-947, Cephalon, Inc. Section 2.7.2 Summary of Clinical Pharmacology Studies. Table A1, pp. 41-42, C25608/1027/BA/US and C25608/1028/BA/US. [b]Tmax expressed as median (range)

- EPIDEMIOLOGY OF FENTANYL ABUSE

Abuse and overdose of fentanyl prescription products (Duragesic, generic fentanyl patches and Actiq) is an increasing public health problem.

Emergency departments in the U.S. saw the number of fentanyl related mentions grow from 28 in 1994, to 1,506 in 2002, according to the most recent numbers available from the Substance Abuse and Mental Health Administration (http://oas.samhsa.gov).

The Drug Abuse Warning Network, (DAWN) tracks drug related emergency room visits nationally. DAWN data document the increasing abuse of fentanyl products, from the years 1997-2002, there were 203 ED mentions of fentanyl products in 1997; 286 in 1998; 337 in 1999; 576 in 2000; 710 in 2001; and 1,506 in 2002.

The number of fentanyl ED mentions documented in the new DAWN for 2004 is also high. Trends cannot be inferred due to major changes to the DAWN system implemented at the beginning of 2003. These changes are the result of a redesign that, among other improvements, altered most of DAWN's core features, including the design of the hospital sample and the cases eligible for DAWN. These improvements create a permanent disruption in trends. As a result, comparisons cannot be made between old DAWN (2002 and prior years) and the new DAWN.

The new DAWN not only captures ED visits associated with substance abuse/misuse, both intentional and accidental, it also captures ED visits related to the use of drugs for legitimate therapeutic purposes. Eight case types are defined in the new DAWN and each case is assigned hierarchically into one case type.

Under the "overmedication" type of case, cases where patients exceeded the prescribed dose of a medication or the recommended dose of an over-the-counter medication are captured. Thus, misuse of a prescription drug or of an OTC medication is captured under the "overmedication" type of case. Cases in which a patient was deliberately poisoned or drugged are classified as "malicious poisoning". Visits classified as case type "other" include pharmaceuticals taken, in general, for non-medical purposes that do not meet the criteria for any other DAWN case type, including pharmaceuticals taken in combination with illicit drugs.

For 2004, DAWN estimates 495,732 (CI: 408,285 to 583,179) ED visits involved non-medical use—i.e., misuse or abuse—of prescription or OTC pharmaceuticals or dietary supplements. Multiple drugs were involved in 57% of these ED visits.[6] ED-related visits that fall into the "overmedication", "malicious poisoning", and "other" categories are aggregated and reported as misuse and abuse ED visits in the new DAWN.

Table 2 displays the number of DAWN ED visits related to misuse and abuse of fentanyl, hydrocodone combinations and oxycodone (single and combination products) as well as prescription data from IMS (National Prescription Audit Plus)[7] to provide a context and crude denominators for the interpretation of DAWN abuse data. Rates of drug abuse ED cases per 100, 000 prescriptions are also presented in **Table 2**.

In 2004 6,493 fentanyl drug abuse related cases were reported to DAWN. For comparison, there were 42,491 reports of hydrocodone combination products and 36,559 reports involving oxycodone (single entity products and combination products). Although DAWN reports fewer (absolute number) of fentanyl ED abuse-related cases relative to oxycodone and hydrocodone, the prescription-adjusted rate of abuse for fentanyl is higher than the comparable, adjusted rates for oxycodone and hydrocodone. **The adjusted rate for fentanyl is 123 ED abuse related cases per 100,000 prescriptions, for oxycodone is 105 per 100,000 prescriptions and for hydrocodone is 37 per 1000,000 prescriptions.**

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[6] Office of Applied Studies. Drug Abuse Warning Network, 2004: National Estimates of Drug-Related Emergency Department Visits. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration, http://DAWNinfo.samhsa.gov/

[7] IMS Health, NPA Plus. Projected Number of total prescriptions dispensed by retail pharmacies including chain, Independent, Food stores, mail order, and long-term care facilities in the US.

Table 2: Estimated DAWN Emergency Department (ED) Visits Relative to Projected Total Number of Prescriptions Dispensed in the U.S.A for Fentanyl, Oxycodone, and Hydrocodone for 2004.

SELECTED DRUGS	ESTIMATED NUMBER OF DAWN ED VISITS[a] 2004	IMS, NPA *PLUS*™ N° RX (000)[b] 2004	RELATIVE NUMBER OF DAWN ED VISITS TO TOTAL NUMBER OF PRESCRIPTIONS
FENTANYL	8,000	—	123
OXYCODONE	36,359	-	105
HYDROCODONE	42,492	—	37

[a]Total mentions for drugs in combination and taken alone. Drug misuse and abuse related visits. **SOURCE:** Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2004 (09/2005 update). [b] IMS Health, National Prescription Audit *Plus*. Not for use outside FDA without prior clearance by IMS America.

DAWN also collects a sample of Medical Examiner Reports of drug-abuse related deaths investigated by medical examiners and coroners. Metropolitan areas that had fewer than 30 drug abuse related deaths in a year were not included, to protect the confidentiality of decedents. The numbers of drug fentanyl abuse related deaths in 28 metropolitan areas listed in DAWN Mortality data for the years 1997-2002 were as follows: 18 in 1997; 43 in 1998; 34 in 1999; 58 in 2000; 75 in 2001; and 140 in 2002.

III – RISKS OF FEBT IDENTIFIED BY THE SPONSOR

The Sponsor identifies and discusses the following risks:

1-Use of the product by non-tolerant individuals: As is the case with other concentrated CII opioid analgesics, individuals using fentanyl who are not tolerant to opioids are at risk of clinically significant and life threatening adverse events such as respiratory depression. This risk is present at the lowest dose and increases with the dose. The Sponsor recognizes that the product must be used only in opioid tolerant patients.

2-Misuse, abuse and diversion: The abuse liability of opioids is known. The pharmacokinetic and pharmacodynamic profile of the formulation is correlated with its abuse liability.

3. *Unintended (accidental) exposure*: The risk of serious consequences from accidental exposure to FEBT is greater in individuals who are not tolerant to opioids.

IV. CSS Analysis of FEBT Risks

The most serious risks of FEBT are: inadvertent, potentially fatal overdose in patients; ingestion/ exposure in the pediatric including adolescent population which carries a high risk of lethality; and overdose associated with misuse and abuse

1. Accidental Overdose in the Patient Population and Vulnerable Populations

The FEBT fentanyl formulation poses risks to the intended patient population as well as to those for whom the product is not intended; children are particularly vulnerable. Patients are at risk of accidental overdose due to variable and unpredictable levels of opioid tolerance, medication errors due to the multiple strengths of similar tablet size and color, underlying disease or drug induced confusion, concomitant medications, and incomplete medical history that might include drug or alcohol abuse. Any pediatric ingestion is likely to be fatal due to the drug's potency, high concentration, and bioavailability. Particularly high risk vulnerable populations are children, adolescents and the elderly.

Specific product properties which contribute to a higher risk of unintentional and accidental overdose are that the tablets, regardless of dose strength/ concentration, are small, round and of similar shape size (1/4 of an inch for the 100 mcg tablet and 5/16 of an inch in diameter for the other strengths). Additionally, the tablets have similar colors) and have a sweet taste

The high bioavailability of FEBT significantly contributes to the serious risk of any overdose, unintentional, accidental or otherwise. FEBT employs the OraVescent® drug delivery technology, which utilizes an effervescent reaction to enhance the rate and extent of fentanyl absorbed through the buccal mucosa. FEBT has no handle to facilitate removal if accidentally placed in the mouth. Once a tablet is placed in the mouth, absorption from the oral mucosa commences rapidly. Hence, even a retrieved tablet (which is highly unlikely) will have delivered a significant dose of fentanyl. If FEBT is swallowed, high plasma concentrations of fentanyl are also reached.

Seriously ill (e.g. cancer) and elderly patients on multiple medications, including other opiate analgesics, are at particular risk for confusion, dosing errors, drug interactions and potentially fatal respiratory depression due to overdose.

- OVERDOSE CASES REPORTED IN CLINICAL TRIALS

Events observed in clinical trials illustrate the risks of respiratory depression and overdose in the intended treatment population. Two cases of respiratory depression were identified in patients enrolled in clinical studies. One patient who was enrolled in an open label study for patients with chronic non-cancer pain, suffered respiratory depression that required intubation and hospitalization. This patient had chronic pain, depression and a previous suicide attempt. According to the case report, after reaching her FEBT maintenance dose, she overdosed on study drug. She denied suicidality and did not report her event in a timely manner to the study investigator. The second patient who required medical intervention,, although not hospitalization, was enrolled in a double-blind study for patients with chronic non-malignant low back pain. This middle aged man apparently overdosed due to confusion about different tablet strengths during the titration period.

2. Overdose associated with Misuse and Abuse

Misuse and abuse of this product is a great concern. In addition to the risks of unintentional accidental exposure to FEBT in children and of overdose in inappropriately selected patients who are non-tolerant or at high risk for confusion, any misuse or abuse, by non-tolerant individuals, and especially by children and adolescents, carries a high risk of fatal respiratory depression.

The risk of respiratory depression also exists in experienced opioid abusers who may be experienced with, and even tolerant, to other less potent opioids. Given the high concentration of fentanyl in each FEBT and its size, the risk of misuse through the intravenous or intranasal routes should be considered greater than for other fentanyl formulations, and other opioid formulations such as Oxycontin.

- MISUSE AND DIVERSION IN CLINICAL TRIALS-

Events observed in clinical trials illustrate the significant risks of misuse, abuse and diversion. Several case reports suggest misuse and abuse; these include reports of theft of study medication as well as poor accountability for study drug.

Detection of aberrant drug use behavior in the controlled setting of a clinical trial is very unusual and raises concern for the safe use of this drug in the general outpatient setting. It is particularly noteworthy in that "high risk patients"---those with a prior history of drug or alcohol abuse-- were reportedly excluded from the clinical trials.

Analysis of the narratives of cases of patients who were withdrawn for reasons coded as "other", "lack of efficacy", "protocol violation", "lost to follow up", or "non-compliance to study medication or procedures" showed several miscoded cases. Included in these cases were patients who reported adverse events of dizziness and drowsiness associated with the study medication that prompted withdrawal from trials.
Symptoms of "dizziness" and "drowsiness" suggest excessive opiate effect and perhaps patients who not tolerant to high potency, high dose opioid medication.

Twenty one subjects exhibited abnormal opioid use (misuse, abuse and suspected addiction) and were discontinued from the studies. Twelve of these subjects were participating in Study 3040 an open-label safety/efficacy study in patients with chronic non-cancer pain and BTP, which enrolled 406 patients. The entry criteria reportedly excluded patients with a prior history of drug or alcohol abuse.

Four instances, two in Study 9915 (open-label safety/efficacy study in patients with cancer and BTP) and two in Study 3040, of theft of the study medication either from patients' homes or cars were identified. In one case, the case report form indicated that a family member was involved in the theft.

The fourteen patients who failed to return study medication were enrolled in Study 3040 the non-cancer pain, open label study. The majority of these cases occurred during the maintenance phase of the trial, after the patients were given 102 tablets of study medication to take home (tablet strength was identified during the titration phase). Issues of study drug accountability in clinical trials is of particular concern. Diversion (loss, theft, etc) in the controlled setting of a clinical trial is rarely detected and signals the high risk posed by FEBT for misuse, abuse, diversion and potentially fatal overdose.

V- EXPERIENCE WITH ACTIQ RMP (SUB PART H)- UNINTENDED PEDIATRIC EXPOSURES TO ACTIQ ,OFF-LABEL USE AND DIVERSION OF ACTIQ

The Actiq RMP requires strict quarterly reporting of all spontaneous reports of unintended pediatric exposures, off-label use and possible diversion. Unintentional pediatric exposures to Actiq have been reported, the majority of which involve toddlers exposed to partially used lozenges or to the applicator handle. In addition off label use is increasing and chain pharmacy call back surveys show that approximately 6% of patients prescribed Actiq are non-opioid tolerant. These findings are of concern considering that FEBT pose a higher risk of overdose.

VI- SUMMARY OF SPONSOR'S PROPOSED RMP

- GOALS AND OBJECTIVES

The goals of the proposed RMP as stated by the Sponsor are:

1. Product should be used only by opioid tolerant individuals
2. Abuse, Misuse and Diversion of Proposed Product should not occur
3. Unintended (accidental) exposure to Proposed Product should not occur

The sponsor discusses the following six objectives of the RMP to accomplish the above goals:

1. Educate practitioners, other healthcare personnel and patients that Proposed Product should only be used by opioid tolerant individuals.
2. Ensure adequate controls are instituted, evaluated, and maintained to prevent the diversion of Proposed Product.
3. Reduce potential abuse, misuse, and diversion of Proposed Product by providing education, ongoing surveillance of abuse, misuse and diversion and cooperating with and providing assistance to law enforcement in the investigations of incidents of abuse or diversion.
4. Reduce or eliminate accidental exposure through product packaging.
5. Educating patients about "safe product use."
6. Reduce or eliminate accidental exposure during storage and to ensure that mechanisms exist to facilitate the prompt return and/or disposal of all unused Proposed Product when it is no longer needed

- SPONSOR LABELING, MEDICATION GUIDE AND KEY MESSAGE IDENTIFICATION

The Sponsor has identified key messages addressing: scheduling status of fentanyl, use in opioid tolerant patients, risk of misuse, abuse and diversion, warnings for children, indication for breakthrough pain in cancer patients and contraindication in acute-pain or postoperative pain.

- SPONSOR EDUCATIONAL EFFORTS

The following general tools are proposed by the Sponsor to manage risks: targeted education & outreach, reminder system, active monitoring, package integrity, blister label and carton label, medication guide, package insert, educational letter [redacted], for physicians, counseling aids, speakers, training for sales representatives, product returns and disposal, reports of diversion and abuse, and blister packages.

The RMP does not contain a proposal for an educational kit to be issued to patients with the first dispensing of medication.

The plan fails to address particularly high risk communities already affected by high rates of narcotic abuse.

- SPONSOR SURVEILLANCE PLAN

The Sponsor proposes the following surveillance activities: active and passive surveillance systems, surveys of physicians, pharmacies, patients, and claims data. DAWN, Monitoring the future (MTF), National Survey on Drug Use and health (NSDUH) data will be monitored and reported. Sponsor will attempt to implement an active monitoring system (e.g., RADARS) at the time of the launch of this product to look for reports of diversion and abuse from launch and subsequent marketing. Reports from the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on this product.

- REPORTING

RiskMAP evaluations will be conducted quarterly for the first two years of marketing with a report of the evaluations submitted to the FDA. Subsequent to this time period, assessment of the RiskMAP will be made on an annual basis and Cephalon will provide the FDA with a report of its progress and any changes they have made to the program.

- SIGNAL IDENTIFICATION

The Sponsor proposes utilizing national pharmacovigilance surveys on drug abuse and diversion, such as DAWN, MTF, NSDUH, to look for any signal or patterns of abuse or diversion associated with this product.

Currently MTF and NSDUH do not collect data on fentanyl, so it is not clear how useful these data bases will be in tracking the use of this product.

- SPONSOR INTERVENTIONS

Six points of intervention were identified for risk management targets: supply chain, point of prescribing, point of dispensing, consumer storage, patient (consumer) use, and disposal of product. The RMP does not list the specifics of proposed interventions for each of the listed targets.

- Physician supervised dose-titration for each patient as performed in the clinical trials.
- Prescribing limited to oncologists and pain specialists.
- Mandatory education for prescribers, patients and caregivers.
- Use of physician and patient/caregiver agreements in setting other than hospital
- Limitations on the quantities of tablets prescribed and dispensed.
- Effectiveness of RMP assessed quarterly for the first two years, based on information collected through active pharmacovigilance and spontaneous reports.

Secondary to the above mentioned at "minimum risk minimization measures", specific recommendations addressing education, surveillance, reporting of events of pediatric exposure, off-label use and diversion, as well as reporting frequency, and intervention are expanded upon in APPENDIX 1

APPENDIX 1:

Recommendations regarding the prevention, surveillance and interventions sections of the RMP

1. The Sponsor should agree as a condition of approval to fulfill the commitments identified in the final RMP.

2. Educational Programs directed to all audiences should include these key messages, in addition to the Sponsor's proposed key messages:

- *Definition of the appropriate treatment population and proper patient selection.* FEBT SHOULD ONLY BE USED BY OPIOID TOLERANT PATIENTS. The Sponsor's proposed black boxed warning should clearly convey this message.
- *Risks and Safety messages.* Physicians and patients must understand and accept responsibility for appropriate use of FEBT. The risks of overdose-- unintentional or otherwise--should be properly addressed and explained.
- *Risks of abuse, diversion, and theft.* Physicians and patients need to know that the high concentration of fentanyl in FEBT makes this product a target for theft and diversion.

3. Develop specific education programs for the prescriber to ensure that the product is used only in opioid tolerant patients utilizing very strict criteria. These programs should also alert the prescriber to inquire about home settings and whether children could potentially be exposed to the product.

4. Patients and families must be educated on the risks and management of adverse effects prior to receiving the first dose of this product. Instructions would warn about the risk of death if a child inadvertently swallowed this medication. Specific education programs would include instructions on monitoring for respiratory depression and how to perform rescue breathing. A physician-patient agreement regarding use of other opioids while taking this product should be considered. The patient must be instructed on proper disposal of unused product.

5. An educational kit should be planned for issue to patients with the first dispensing of product. The contents of the kit need to be described in the RMP. A method of surveying patients who have received this kit must be devised to measure the effectiveness of this strategy.

6. Plans to address risk to communities already affected by high rates of narcotic abuse (West Virginia, Kentucky, Maine) must be developed. Special groups (teenagers) at risk of abusing this formulation must be targeted for education using visual devices and other special education programs. Specific plans to address health care societies must be described.

7. Sales representative training for this drug must be described. All promotional and educational materials should be submitted for prior review.

8. The Sponsor should be instructed to report any reports related to pediatric and adolescent exposures regardless the outcome or intent, off label use, misuse, and diversion to the FDA. Reporting frequency to the FDA needs to be defined.

9. The RMP should include specifics on how the Sponsor plans to monitor who is actually prescribing this product, how these restrictions will be enforced, and what will happen if other providers (e.g. dentists) start prescribing this drug. The product should only be dispensed from a central pharmacy. Tamper resistant mandatory prescription pads should be distributed for this product. A patient registry should be established and maintained to track individual doses of this product.

10. In the clinical studies supporting this product, the first dose of medication was given in the physician's office and the patient monitored for adverse effects. This restriction should be a requirement for prescribing this dosage form. The first dose of medication should be given in the physician's office and the patient monitored for adverse effects.

11. Address the issues of accidental overdose in patients and unintended users. Specific plans need to be developed to actively monitor for these cases. DAWN "live" may be a useful tool to monitor for ED abuse related cases. The Sponsor should plan to monitor and submit reports from medical examiners, toxicology and poison control centers.

12. Develop a plan to contract with large pharmacies to survey patients receiving the proposed product to collect information about use, opioid tolerance, welcome kit and other RMP measures.

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/s/

Corinne Moody
5/17/2006 11:21:00 AM
CSO
Corinne Moody for Geoffrey Zeldes, M.D.

Silvia Calderon
5/17/2006 11:22:03 AM
CHEMIST

Deborah Leiderman
5/17/2006 11:25:32 AM
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 9, 2006

To: Bob A. Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology (HFD-170)

From: Deborah B. Leiderman, M.D., Director
Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: Executive Summary[1]
NDA 21-947. Fentanyl Citrate Effervescent Buccal Tablets (100, 200, 400, 600 and 800 mcg)
Sponsor: Cephalon, Inc.

This memorandum responds to a consultation from the Division of Anesthesia, Analgesia and Rheumatology products, HFD-170, concerning the risks of Fentanyl Buccal Tablets (NDA 21-947, Cephalon) as well as a review of the Sponsor's proposed Risk Management Plan (RMP). CSS has reviewed the pertinent sections of the NDA including clinical pharmacology and safety, chemistry, product formulation, clinical trial databases, and proposed RMP.

EXECUTIVE SUMMARY

The fentanyl effervescent buccal tablet product (FEBT) is a highly concentrated, high-dose, highly bioavailable, rapid onset formulation of one of the most potent mu opioid agonists. Fentanyl is estimated to be eighty times as potent as morphine as an analgesic (Reisine and Pasternak in Goodman & Gilman).[2] NDA 21-947 proposes five tablet strengths (100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg) for buccal mucosal administration all indicated for "the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain."

Fentanyl is controlled in Schedule II of the Controlled Substances Act (CSA) as are similar opiates approved for medical use including hydromorphone, morphine, and oxycodone. Schedule II drugs have the highest potential of abuse and pose a high risk to the public health (21 U.S.C. 812).

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[1] Full consultation to follow in separate document.
[2] Reisine, T. and Pasternak, G. Opioid Analgesics and Antagonists. In Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, 1996.

The risks of unintentional potentially fatal overdose, as well as of misuse or abuse of fentanyl, and of FEBT in particular, are extremely high, even when compared to risks posed by other fenantyl products such as Actiq (oral transmucosal fentanyl citrate).

Actiq was approved in 1998, under Subpart H regulations; implementation of a Risk Management Plan (RMP) was a condition of approval. The Actiq RMP requires strict quarterly reporting of all spontaneous reports of unintended pediatric exposures, off-label use and possible diversion. Unintentional pediatric exposures to Actiq have been reported, the majority of which involve toddlers exposed to partially used lozenges or to the applicator handle. Ready detection and intervention in these exposures was facilitated by the visible applicator stick. The FEBT formulation, in contrast, lacks Actiq's applicator stick for ready retrieval of the product from a child's mouth and produces very high fentanyl plasma levels when ingested or swallowed.

Pharmacokinetic characteristics of FEBT that increase its risks includes its higher bioavailabilty relative to Actiq (65% ±20 % vs 47% ± 11%) and highly variable individual Tmax, which is unrelated to tablet strength and ranges from 20 minutes to three hours across all dosage strengths.[3]

This new fentanyl formulation, FEBT, poses additional risks to the intended patient population and to the public health. At particular risk are the vulnerable populations of children, including adolescents, and the elderly. Patients are at risk of accidental overdose due to variable and unpredictable levels of opioid tolerance, medication errors related to multiple FEBT strengths of similar tablet size and color, disease-related or drug induced confusion, concomitant CNS depressant medications, and incomplete medical history that might include drug or alcohol abuse. Any accidental pediatric ingestion is likely to be fatal due to the product's high concentration and high bioavailability. Misuse of the formulation by recreational abusers as well as by patients carries a high risk of lethality.

The risk of fatal overdose due to respiratory depression exists even in active opioid abusers who may be regular users of and tolerant to other less potent opioids. The fact that no crushing or extraction of fentanyl from the dosage form is required to rapidly achieve high fentanyl plasma levels will appeal to abusers and misusers; consequently this increases the probability of abuse and potentially fatal outcome. Misuse of FEBT through the intranasal or intravenous routes is more likely than for other fentanyl products (and greater than for other high concentration opioid analgesic products such as Oxycontin).

Events observed in clinical trials illustrate the significant risks of overdose, misuse and abuse from FEBT. Two cases of respiratory depression were identified in patients enrolled in clinical studies, requiring hospitalization in one case. One patient enrolled in

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[3] Clinical Pharmacology and Biopharmaceutics Review. Chandra S. Chaurasia, Ph.D. and Suresh Doddapaneni, Ph.D.,OCPB Division: Division of Clinical Pharmacology. DFS-NDA#21-947

an open label study for patients with chronic non-cancer pain suffered respiratory depression that required intubation and hospitalization. [4] The second patient, a middle-aged male, enrolled in a double-blind study for patients with chronic non-malignant low back pain, became unresponsive and required medical intervention due to inadvertent overdose. Several other case reports suggest misuse and abuse; these include reports of theft of study medication as well as poor accountability for study drug.

Detection of aberrant drug use behavior in the controlled setting of a clinical trial is very unusual and raises concern for the safe use of this drug in the general outpatient setting. It is particularly noteworthy in that "high risk patients" ---those with a prior history of drug or alcohol abuse-- were reportedly excluded from the clinical trials.

The Sponsor proposed a Risk Management Program (RMP) to minimize three identified risks: 1) use of the product by non-tolerant individuals; 2) misuse, abuse and diversion; and 3) unintended exposure. The Sponsor's RMP relies on education of stakeholders (labeling and information for patients, physicians and pharmacists) and supporting educational materials.

CONCLUSIONS

- FEBT poses significantly greater risks than other currently marketed, concentrated Schedule II opioid analgesic drug products.
- The risks associated with FEBT include potentially lethal overdose in the intended patient population as well as in non-patients. Vulnerable populations at high risk include children, adolescents and the elderly.
- The risk of fatal overdose due to respiratory depression is greater with FEBT than for Actiq, which was approved under Subpart H.
- The abuse liability of this particular fentanyl formulation is extremely high, even when compared to existing fentanyl products such as Actiq and Duragesic.
- Aberrant behavior (stolen drug, drug abuse, and problems with trial drug accountability) observed in clinical trials is of grave concern as it is predictive of post-marketing risks.
- The sponsor's RMP is deficient in the areas of risk assessment and prevention, identification of key messages, educational plans, surveillance methodology, signal detection and interventions.
- The Sponsor's RMP which largely relies on education and signal detection cannot adequately manage the risk of the product

[4] This patient had chronic pain, depression and a previous suicide attempt. After reaching her maintenance dose, she overdosed on study drug, required intubations but denied suicidality and did not report her event in a timely manner.

RECOMMENDATIONS

It is not clear that all the measures necessary to support the safe use of this product can be implemented in the outpatient setting.

At a minimum the following measures should be implemented:

- Physician supervised dose- titration for each patient as performed in the clinical trials.
- Prescribing limited to oncologists and pain specialists.
- Mandatory education for prescribers, patients and caregivers
- Use of physician and patient/caregiver agreements.
- Limitations on the quantities of tablets prescribed and dispensed.

Specific recommendations addressing education, surveillance, reporting of events of pediatric exposure, off-label use and diversion, as well as reporting frequency, and intervention are expanded upon in the full CSS consultation.

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/s/

Silvia Calderon
5/9/2006 01:02:20 PM
CHEMIST

Deborah Leiderman
5/9/2006 01:07:51 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-947

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fentanyl effervescent buccal tablets.

We also refer to your submission dated September 16, 2005, submitted as serial # 055 to your IND 65,477 for this product requesting review of the trade name for this product.

The Office of Drug Safety's (ODS) Division of Medication Errors and Technical Support (DMETS) review of your proposed trade name is complete and we have the following comment.

> The tradename is unacceptable . Please submit an alternate proprietary name for your product.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 28, 2006

TO: Kim Compton, Regulatory Project Manager
Robert Shibuya, M. D., Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-947

APPLICANT: Cephalon Inc.

DRUG: Oravescent (fentanyl effervescent buccal tablets)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: [redacted]

CONSULTATION REQUEST DATE: November 3, 2005

DIVISION ACTION GOAL DATE: April 30, 2006

PDUFA DATE: June 30, 2006

I. BACKGROUND:

Fentanyl citrate is a potent opioid analgesic with rapid onset and short duration of action. It has a profile of pharmacological effects similar to morphine. It is used primarily as an analgesic for the control of pain associated with all types of surgery. Fentanyl citrate referred to as ORAVESCENT fentanyl has been developed as an alternate system for the transmucosal delivery of fentanyl. ORAVESCENT fentanyl citrate is a tablet designed for placement and retention within the oral cavity for a period sufficient to allow for disintegration of the tablet and absorption of a therapeutically useful amount of fentanyl across the oral mucosa. The placement in the oral cavity causes the tablet to disintegrate in a relatively short amount of time. The sponsor is seeking approval of this form of fentanyl citrate (fentanyl effervescent buccal tablets) under the assumption that effervescence helps the absorption of fentanyl across the oral mucosa when

compared to ACTIQ, a lozenge dosage form designed for oral transmucosal administration. The delivery of ORAVESCENT fentanyl formulation is passive and does not require the patient to actively maneuver the tablet around the mouth.

The review division requested inspection of the following four protocols:

Protocol Study 099-14: A Multicenter, Double-Blind, Placebo-Controlled Study of ORAVESCENT Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients.

Protocol Study 099-15: A Multicenter, Open-Label, Long-Term Study of ORAVESCENT Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients (safety study).

Protocol Study C25608/3039: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of ORAVESCENT Fentanyl Citrate in Opioid-Tolerant Patients With Cancer and Breakthrough Pain

Protocol Study C25608/3040: An Open-Label, 12-Month Study to Evaluate the Safety, Tolerability, and Efficacy of ORAVESCENT Fentanyl Citrate for the Management of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Noncancer Pain (safety study).

Four sites were selected for data audit in support of this application. Two sites were selected to cover protocols 14, 15, and 3039; one site was selected to cover protocols 14, 15, 3039, and 3040; and one site to cover protocol 14.

II. RESULTS (by protocol/site):

Name of CI and site #. if known	City, State*	Protocol	Insp. Date	EIR Received Date	Final Classification
		14,15,3039	2/17/06	4/10/06	VAI
		14,15,3039	3/6/06	4/3/06*	NAI/pending
		14, 15, 3039,3040	1/24/06	4/7/06*	VAI/pending
		14	1/12/06	3/31/06*	NAI/pending

* based on e-mail summary statement from field investigator

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocols 14, 15, and 3039

1.

At this site a total of 23 subjects were screened and enrolled in three protocols (099-14, 13 subjects; 099-15, 7 subjects; and C25608/3039, 3 subjects). For study 099-14, all subjects' files were examined for informed consent and no regulatory violations found. The medical records were reviewed in depth and compared to case report forms and to data listings for primary efficacy endpoint and adverse events for 13 subjects.

For study 099-15, all subjects' files were reviewed for informed consent and no regulatory violations were found. The medical records were compared to source data, case report forms and data listings for seven subjects and no significant findings were noted [except for subject #10 who received an investigational drug (Venofer) while on this study].

The records for all three subjects enrolled in study protocol 3039 were reviewed and no regulatory violations were found.

A Form FDA 483 was issued at the close of the inspection. Significant inspectional findings were as follows: Six subjects (001, 008, 020, 021, 022, and 023) enrolled in study 099-14 were not titrated to an acceptable dose in order to achieve adequate pain relief at 30 minutes; subject 017 enrolled in study 14 did not receive an adequate dose of morphine or its equivalent to qualify for admission; and the medical records for subject 010 showed that this subject was inappropriately continued in study 099-15 after being enrolled in another study of an investigational drug (Venofer) for anemia at the same time the subject was enrolled in study 15. The clinical investigator acknowledged the inspectional observations.

In general, the records reviewed were accurate and no significant problems were found that would adversely impact the acceptability of results. The adverse events experienced by subjects during the studies were accurately reported in the case report forms.

The data appear acceptable in support of the pending application.

2. _____

Observations noted below are based on an email summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site a total of 32 subjects were screened and enrolled in three protocols (099-14, 10 subjects; 099-15, 12 subjects, and C25608/3039, 10 subjects). For study 099-14, ten subjects were screened, four subjects withdrew their consent, and two subjects were discontinued. Subject #004 experienced an adverse event after increasing study medication to 800 ug during titration and had difficulties completing diary and elected to withdraw his consent. Subjects 005 and 009 did not experience breakthrough pain and were dropped. Subject 008 was discontinued during the titration phase. Five subjects (001, 002, 003, 006, and 010) completed the study and rolled over study to 099-15. Subject 010 experienced fatigue, mucositis, SOB, constipation and anorexia; subject 001 experienced anorexia; and subject 03 experienced swelling and numbness of fingers. These events were not reported in the case report form because the events were considered disease-related.

For study 099-15, twelve subjects were screened; eight subjects were rolled over who completed protocols 099-14 and 3039. Four subjects were newly screened, with two screen failures, one referred to hospice, and one randomized. The following subjects were discontinued: subjects 002, 004, and 006 withdrew consent, and subjects 010 and 304003 died from metastatic lung and ovarian cancer, respectively. The medical records for all subjects in study 099-15 were compared to source data, case report forms and data listings and no regulatory violations found.

For study C25608/3039, ten subjects were screened and enrolled under this protocol. Three subjects were reported as screen failures. One subject withdrew due to adverse event (nausea), and three subjects completed the double blind portion of the study. The medical records/source data for all randomized subjects were reviewed and the source data were compared to case report forms and to data listings for primary efficacy endpoints and adverse events. Subjects' files for informed consent were reviewed and no regulatory violations found. The adverse events experienced by subjects during the study were accurately reported in the case report form (except for subject 010 who rolled over to study 099-15 and died suddenly for disease progression). In general, the

records reviewed were accurate, although a few records were reportedly destroyed during the hurricane season, and no significant problems were found that would impact the results. There were limitations to this inspection in that some records were destroyed by hurricane.

The data appear acceptable in support of the pending application.

B. Protocols 14, 15, 3039, and 3040

1.

Observations noted below are based on an email summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site, a total of 45 subjects were screened in protocols 099-14, 099-15, C25608/3039, and C25608/3040. Forty subjects were enrolled; thirteen were discontinued; five were screen failures; nineteen continued; and eight subjects completed the studies. Study 099-14 was closed at the time of the inspection. Of the subjects enrolled, three to four subjects' files from each study were reviewed. The medical records for all enrolled subjects were reviewed in depth and were compared to case report forms and data listings for primary efficacy endpoint and adverse events.

For studies 099-15 and C25608/3039, all subjects' files were reviewed for informed consent and no significant problems were found. The medical records were reviewed and compared to case report forms and data listings, and no problems were found.

The inspection found that subject 49003 enrolled in study 14 did not have a hematology panel done prior to entry. For study 3040, 2 subjects (032001 and 032003) were moved to the long-term maintenance treatment period although they did not demonstrate that a successful dose was achieved. The adverse events experienced by subjects during the studies were accurately reported in the case report forms. A Form 483 was issued for enrollment of three ineligible subjects into studies 14 and 3040. The clinical investigator acknowledged the inspectional observations. In general, the records reviewed were accurate and no regulatory violations were found that would adversely impact acceptability of the results.

The data appear acceptable in support of the pending application.

C. Protocol 14

1.

Observations noted below are based on an email summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Nine (9) subjects were enrolled at this site; nine completed the study. The records for all nine subjects were reviewed. No regulatory deviations were noted. No FDA 483 was issued.

The data appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs , did not identify any significant observations that would compromise the integrity of the data. As noted above, observations related to Drs. are based on an email summary from the FDA field investigator; the EIRs for these inspections are currently pending. Overall, the data appear acceptable in support of the pending

application. Should any of the pending EIRs contain additional information that would affect the application, the information will be forwarded to the review division as soon as it becomes available.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Constance Lewin
4/28/2006 05:28:59 PM
MEDICAL OFFICER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

THROUGH: Gerald Dal Pan, M.D., M.H.S. Director
Office of Drug Safety

FROM: ODS Fentanyl Buccal Tablets RiskMAP Review Team

DRUG: Fentanyl Buccal Tablets, NDA 21-947

APPLICANT: Cephalon, Inc.

SUBJECT: Review of Risk Minimization Action Plan, submitted August 31, 2005

PID: D050554

1 EXECUTIVE SUMMARY

This consult follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Drug Safety (ODS) to review and comment on the Risk Minimization Action Plan (RiskMAP) for Fentanyl Buccal Tablets submitted by Cephalon as part of its new drug application (NDA 21-947). Fentanyl Buccal Tablet is an opioid analgesic that will be available in five dosage strengths, 100, 200, 400, 600, and 800 mcg. The proposed indication is for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. The Fentanyl Buccal Tablet RiskMAP utilizes labeling as well as healthcare professional and patient education and planned surveillance activities.

We agree with the Sponsor's plan to educate patients and healthcare professionals about the risks of Fentanyl Buccal Tablets, however we do not believe that education alone will be adequate in addressing the risk of accidental overdose in children or the risks of inadvertent overdose from a medication error or use of Fentanyl Buccal Tablets in opioid naïve patients.

We recommend use of mandatory patient education in the form of a Medication Guide (MG). Fentanyl Buccal Tablets appear to meet the requirement of filling at least one of three possible criteria for a MG (CFR 208.1(c)(1)), specifically, that patient labeling could prevent serious adverse events.

We additionally recommend that consideration be given to limiting marketing and promotion of Fentanyl Buccal Tablets to facilitate labeled use. The Sponsor needs to also take measures to prevent the potential for accidental overdose in children and medication errors by conveying important safety messages in the boxed warning, adding warnings to the carton and container labeling, testing the container color scheme with practicing health care professionals, revising the dosing conversion recommendations so that they follow a systematic conversion across all strengths, and revising several tablet colors to avoid confusion. These recommendations as well as recommendations on the Sponsor's Education Plan and Pharmacovigilance/Evaluation Plan are described in more detail in Section 6 of this document.

2 BACKGROUND

Fentanyl Buccal Tablets is a potent rapid onset opioid analgesic that employs a proprietary fast-dissolve drug delivery technology called OraVescent (OVF). Fentanyl Buccal Tablets is placed between the superior gum and cheek lateral to the first or second molar. Upon placement in the buccal cavity, the tablet rapidly disintegrates, allowing drug to be released from the tablet matrix and absorbed across the oral mucosa. There are five proposed dosage strengths, 100, 200, 400, 600, and 800 mcg.
The proposed indication for Fentanyl Buccal Tablets is for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. Its use is contraindicated for management of acute or post-operative pain.

The enhanced absorption obtained with Fentanyl Buccal Tablets compared to the marketed Actiq® (oral transmucosal fentanyl citrate) will allow therapeutic concentrations in plasma to be achieved at a lower total dose of fentanyl citrate in the delivery system. According to the Clinical Pharmacology Review[1] the fraction of the Fentanyl Buccal Tablets "dose absorbed transmucosally is approximately 50% of the total dose compared to that of approximately 25% from Actiq resulting in a higher absolute bioavailability (65%±20%) when compared with Actiq (47%±11%). Based on these comparisons, an approximately 30% smaller dose of OVF has been suggested to achieve systemic exposures comparable with those following administration of Actiq. It is noted that absolute bioavailability of OVF taken orally is only 31% ±13% and any unintentional swallowing of the OVF tablets would provide far lower exposure than that from the same dose administered through the intended buccal route."

[1] Chaurasia, CS. Clinical Pharmacology and Biopharmaceutics Review. NDA 21-947 Fentanyl Citrate Effervescent Buccal Tablet; dated March 16, 2006.

3 SAFETY CONCERNS

The Sponsor has identified the following three risks that the proposed RiskMAP is to address (from Sponsor's submission):

- Use in Opioid Naïve Patients: Individuals using fentanyl citrate who are not tolerant to opioids are at risk for clinically significant and life-threatening adverse events such as respiratory depression. The risk is present at any dose in such individuals and the risk increases with dose. By limiting the use of Fentanyl Buccal Tablets to those already taking opioid products, the risk of serious outcomes may be minimized.
- Unintended (accidental) exposure: The risk of serious consequences from accidental exposure to Fentanyl Buccal Tablets is greater in individuals not tolerant to opioids especially accidental ingestion by children.
- Misuse, abuse and diversion: Fentanyl is a known drug of abuse, and the Fentanyl Buccal Tablets dosage form (effervescent buccal tablets) has the potential to be abused. The pharmacokinetic and pharmacodynamic profile can influence its abuse liability.

While these risks must be addressed by the RiskMAP, ODS has identified additional risks posed by this product that may be unique to this formulation. These concerns are briefly discussed below and in section 5 of this review.

- **Potential for Accidental Exposure in Children** - We are concerned that this product may be mistaken for candy due to the size and color of the tablets. We also note the [redacted] cause the tablet to have a sweet taste. Because these tablets may be more attractive to children it is imperative that all precautions be taken to ensure the product is kept out of the reach of children.
- **Potential for off-label use** - We are concerned that this product may be prescribed and used in opioid naïve patients. Because of the relatively large amount of the highly potent fentanyl in each tablet, opioid-naïve patients are at an increased risk of opioid overdose, respiratory depression and death if exposed to this product.
- **Potential for Medication Errors** - The introduction of this Fentanyl Buccal Tablet may result in medication errors. Errors may arise due to a knowledge deficit among health care providers concerning awareness of the availability of this new product and differences in bioavailability between the currently marketed Actiq and Buccal Tablet. Confusion may also arise from the current labeled dosing conversion, similar tablet colors, and similar color scheme used for strength differentiation on Actiq and Fentanyl Buccal Tablet. These potential errors are described in greater detail in section 6 of this review.

4 SPONSOR'S PROPOSED RISKMAP

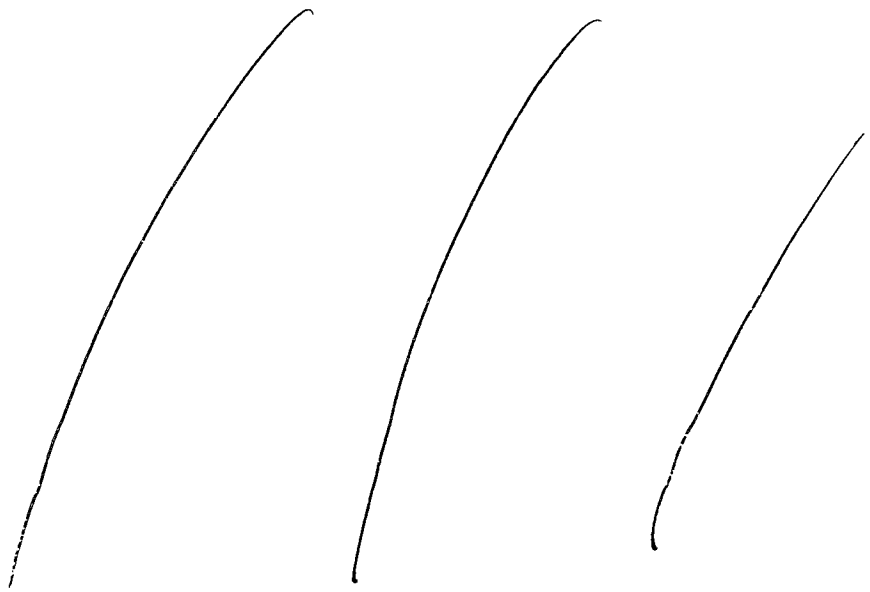
The Sponsor's goals of the proposed RiskMAP are as follows (from Sponsor's submission):

- Fentanyl Buccal Tablets should be used only in opioid tolerant individuals
- Abuse, misuse and diversion of Fentanyl Buccal Tablets should not occur
- Unintended (accidental) exposure to Fentanyl Buccal Tablets should not occur

The Sponsor proposes to meet these goals utilizing professional and patient labeling, healthcare provider and patient education, and surveillance. These are described in more detail below.

4.1 PROPOSED LABELING

The Sponsor is proposing the following boxed warning outlining the appropriate patient population and potential risks associated with effervescent fentanyl.



The sponsor proposes to contraindicate its use in the management of acute or postoperative pain and in opioid non-tolerant patients.

4.2 TARGETED EDUCATION AND OUTREACH

The Sponsor plans a targeted education and outreach program directed at patients, physicians, and pharmacists.

4.2.1 Healthcare Professional Education

Healthcare professional educational is directed at physicians and pharmacists. The education tools include the package insert, direct risk communication by Cephalon field

representatives, educational introductory letter to physicians and pharmacist, [redacted], PharmAlert for retail pharmacists, counseling messages, counseling aids, and educational material/speaker training for professional societies. They also state that Cephalon field representatives will receive product-specific training.

4.2.2 Patient Education

The educational tools directed at the patient include using [redacted] carton label and a [redacted] Medication Guide).

4.2.3 Additional Tools

Fentanyl Buccal Tablets will be marketed as a Schedule II drug.

Cephalon will accept returns for disposal of unwanted Fentanyl Buccal Tablets to minimize the amount of excess product available.

Tablets will be supplied in double foil blister child resistant packaging to minimize the risk of accidental exposure. Poison Control number will be provided for accidental ingestion.

5 SPONSOR'S PROPOSED PHARMACOVIGILANCE/EVALUATION PLAN

The Sponsor describes their plan to employ surveillance and monitoring techniques targeted at prescribers, pharmacists, and patients to assess the effectiveness of the education and reminder tools at the point of intervention.

5.1 ACTIVE AND PASSIVE SURVEILLANCE SYSTEMS

Cephalon plans to utilize the Toxic Exposure Surveillance System (TESS), the Drug Abuse Warning Network (DAWN), and monitoring of publications to augment their pharmacovigilance system.

The Sponsor is also considering an active surveillance system (similar or the same as RADARS) to identify the use patterns of the product.

5.2 SURVEYS OF PATIENTS, PHYSICIANS, AND PHARMACISTS

The Sponsor plans to conduct three separate survey systems targeted at the three principal intended audiences: prescribers, pharmacists, and patients. These surveys will be repeated every six months for the first two years of the program.

- Surveys of physicians will be designed to evaluate their knowledge of and use of Fentanyl Buccal Tablets.
- Surveys of pharmacists will include assessments of their knowledge of the risks associated with Fentanyl Buccal Tablets, the indication and their awareness and use of the carton checklist, medication guide, and other information about the product.

- Surveys of patients will include assessments of their knowledge of the risks associated with Fentanyl Buccal Tablets, the indication, directions for use, and receipt of and perceived utility of the medication guide and other counseling tools.

5.3 CLAIMS DATA

Cephalon will purchase claims data as a surveillance tool to monitor prescribing to assess the degree to which Fentanyl Buccal Tablets are being prescribed only to opioid-tolerant patients.

5.4 OTHER SURVEILLANCE ACTIVITIES

The Sponsor plans to employ interventions such as education or outreach initiatives if during their surveillance they identify significant abuse or diversion within a geographic area.

The Sponsor plans to cooperate and assist law enforcement agencies at a federal, state, and local level in cases of abuse or diversion.

6 ODS CONCERNS, COMMENTS, AND RECOMMENDATIONS

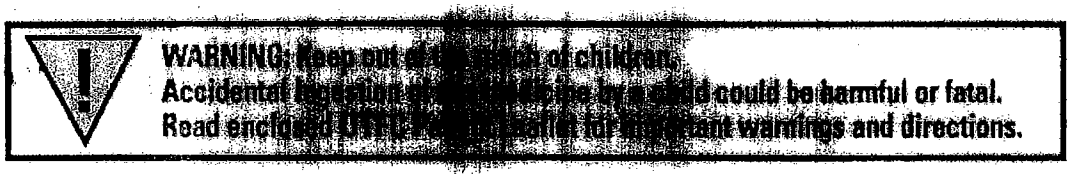
The Sponsor has proposed to address the risks of accidental exposure, use in opioid naïve patients, and misuse and abuse of Fentanyl Buccal Tablets with a RiskMAP that focuses on education of healthcare providers and consumers. The Sponsor's current proposal to minimize the risks associated with Fentanyl Buccal Tablets may not go far enough in addressing the additional risk issues outlined below.

Below, we discuss our concerns with this product and possible risk management considerations as well as comments and recommendations to the Sponsor's current proposed RiskMAP and Pharmacovigilance Plan. Some of these concerns and recommendations were conveyed to the Sponsor during a teleconference on March 31, 2006. The remaining comments were provided to the DAARP to share with the Sponsor.

6.1 POTENTIAL FOR ACCIDENTAL EXPOSURE IN CHILDREN

We are concerned that this product may be mistaken for candy due to the size and color of the tablets. We also note the product [redacted] will cause the tablet to have a sweet taste. Because these tablets may be more attractive to children it is imperative that all precautions be taken to ensure the product is kept out of the reach of children. We acknowledge the testing performed by the sponsor to ensure the container closure is child-resistant. However, the warning statement to keep out of the reach of children appears in small black print on the carton labeling and crowded with other text. As labeled this statement could be easily overlooked. To help bring prominence to this statement:

- We recommend revising the carton labeling so that a warning statement appears boxed and in bold type. It should have a similar appearance to the warning below that appears on the Actiq labeling, but written in consumer-friendly language for easier comprehension.



We were also concerned with the possibility of residue remaining in opened blister packaging leading to accidental drug exposure. However, the sponsor confirmed that no residue remained in the opened blister packaging during a March 31, 2005 telecon.

6.2 Potential for Use in Opioid Naïve Patients

Because of the relatively large amount of the highly potent fentanyl in each tablet, opioid-naïve patients are at an increased risk of opioid overdose, respiratory depression and death if exposed to this product. We acknowledge that Actiq contains more micrograms of fentanyl per dosage form. However, it is less bioavailable than Fentanyl Buccal Tablets.

- We recommend that the Sponsor restrict advertising and promotional activity of Fentanyl Buccal Tablets to those physicians that care for cancer patients in order to limit prescribing to cancer patients who are opioid tolerant.

6.3 POTENTIAL FOR MEDICATION ERRORS

The introduction of this Fentanyl Buccal Tablet may result in medication errors. Errors may arise due to a knowledge deficit among health care providers concerning awareness of the availability of this new product and differences in bioavailability between the currently marketed Actiq and Fentanyl Buccal Tablet. Confusion may also arise from the current labeled dosing conversion, similar tablet colors, and

6.3.1 Bioavailability

The Fentanyl Buccal Tablet is approximately 2 times as potent as the oral transmucosal system. Knowledge of these key differences is required to ensure the proper strength is prescribed, dispensed and administered to the patient. The warning included in the is not adequate to ensure the understanding of these key differences.

We recommend the following:

- Include a statement in the Boxed Warning concerning the differences in product bioavailability.

- Include a Boxed Warning on the container label and carton labeling that conveys the products cannot be substituted on a microgram per microgram basis. This statement should also refer them to the Dosage and Administration section of the labeling for instruction on proper conversion between these product formulations.
- The Sponsor should test key safety messages in practicing heath care professionals to determine the wording that will best convey this key message.

6.3.2 Product Conversion

Dosing conversion between the Fentanyl Buccal Tablets and Actiq is not dependent on their 2:1 bioavailability ratio. For example, when converting a patient from 400 mcg of Actiq the starting dose for the buccal tablet is 100 mcg and not the expected 200 mcg. Moreover, the dosing conversion chart supplied in the Dosage and Administration section of the package insert is confusing. The conversion follows a non linear approach to product conversion at the higher strengths. This nonlinear approach will require memorization by health care providers and thus may lead to dosing errors.

To avoid this type of confusion, we recommend:

- Revising the dosing conversion recommendations so that they follow a systematic conversion across all strengths.

6.3.3 Container and Carton Coloring

The Sponsor uses a color scheme to differentiate the buccal tablet strengths. However, this color scheme is

- We recommend that the Sponsor test this color scheme with practicing health care professionals to ensure the colors do not convey an unintended meaning and to ensure that the carton labeling offers a distinct look to avoid product selection errors.

6.3.4 Tablet Coloring

We are concerned with the color similarities between the lowest strength buccal tablet of 100 mcg and the highest strength tablet of 800 mcg . Many patients and health care providers use the tablet color as verification of the correct dosage strength. Although the sponsor includes a note in the How Supplied section of the insert

labeling that states "Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing." We believe the color similarity may interfere with this color verification.

We are concerned with the proposed tablet color for the 600 mcg buccal tablet. The labeling indicates the 600 mcg tablet will be

To avoid confusion among these product strengths, we recommend the following:

- The sponsor should revise the tablet color of the 600 mcg buccal tablet to avoid confusion with the
- We recommend revising either the 100mcg, 200mcg or 800mcg, to a non overlapping color.

6.4 *RECOMMENDATIONS ON SPONSOR'S EDUCATIONAL PLAN*

- We recommend a medication guide (MG) as per the DAARP/ODS teleconference with Cephalon on March 31, 2006. The MG should instruct patients about the risks of respiratory depression and how to identify the symptoms of opioid-induced respiratory depression. The MG should also alert patients that the two oral fentanyl products (Fentanyl Buccal Tablets and Actiq) cannot be interchanged on a mcg per mcg basis.
- The Health Care Provider Education should include plans to ensure:
  - Practitioners understand that the oral fentanyl products are not equivalent on a mcg to mcg basis. Fentanyl Buccal Tablet has twice the bioavailability of the oral transmucosal system.
  - Conversion between products is not based on product bioavailability. For example when converting a patient from 400 mcg of the oral transmucosal product, the starting dose for the buccal tablet is 100 mcg and not 200 mcg, etc. Moreover, the dosing conversion between products does not employ a consistent ratio across the dosing range.
  - This product is not intended for use in opioid naïve patients
  - Understand and counsel patients on the proper administration of this drug (e.g., correct placement of the tablet in the mouth; instructions not to chew or swallow the tablet).
- The Patient Education should include plans to ensure:
  - Patients are educated to understand that these two oral fentanyl products are not the same and cannot be interchanged on a mcg per mcg basis or used concomitantly
  - Understand the proper administration of this drug (e.g., correct placement of the tablet in the mouth; instructions not to chew or swallow the tablet)
- See Appendix 1 for FDA requests for clarification relating to the educational plan. Sponsor's response will not be considered as part of the FDA review cycle.

6.5 *RECOMMENDATIONS ON PHARMACOVIGILANCE/EVALUATION PLAN*

6.5.1 Postmarketing Reporting

- We request that the Sponsor submit the following as Postmarketing 15-day Alert Reports:
    - Any report with an outcome of death.
    - Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome.
    - Any medication error[2] reports regardless of patient outcome
- The Sponsor should include a special section in the descriptive portion of their quarterly Periodic Reports describing the status of any efforts and data relating to their risk management plan. This section should include (but not be limited to) available data on the following:
    - Extent of use (denominator estimates)
    - Indicators of off-label use or inappropriate prescribing (i.e. opioid-naive)
    - Summary of reports involving medication errors and inadvertent pediatric exposures
    - Summary of adverse events involving opioid naïve patients
    - Rates of misuse, abuse; addiction or diversion observed
    - Results of any investigation or surveys conducted
    - Outcome of any interventions, such as targeted educational interventions and antidiversion programs conducted.

6.5.2 Survey Methodology

The Sponsor should submit a more detailed description of their survey methodology, which includes (but is not limited to) answers to the following questions:

- Who will receive the survey, how will the sample be determined, and what are the selection criteria?
- What controls will they use to minimize bias?
- What controls will they use to compensate for the limitations associated with their methodology?
- How many physicians/pharmacists/patients will be surveyed?
- How will the survey be administered?
- What questions will be posed on the survey instrument?

The sponsor also indicates in the RiskMAP that these surveys will be conducted every 6 months for two years, and that the sponsor will reevaluate the RiskMAP for possible modification.

---

[2] "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.": http://www.nccmerp.org/aboutMedErrors.html

- The sponsor needs to clarify if this reconsideration of the RiskMAP will occur with each 6 month evaluation, or at the end of the two year survey period. Please also clarify how this information will be conveyed to FDA.

6.5.3 Claims Data

The sponsor proposed to use claims data to monitor prescribing patterns.

- We recommend the claims data provide adequate on patients' opioid tolerance.

6.5.4 Literature review

- The Sponsor's literature review should include a review of case reports and studies that specifically address safety concerns.

6.5.5 Review of National Surveys

- The sponsor proposes utilizing national surveys to find signals or patterns of abuse and diversion of their product. Their proposal includes the following limitations:
    - The Sponsor proposes using the Drug Abuse Warning Network (DAWN) to track adverse events and proposes
      Pharmaceutical firms have access to DAWN *Live!* via an online query system and may receive information on an as needed basis. The sponsor has not provided information on how often they plan to access this information, nor what benchmarks will be used to detect a safety signal. Comparing their fentanyl product requires utilization on all comparators to be included in these comparisons.
    - Monitoring the Future (MTF) data which collects data on secondary school students, college students, and young adults currently does not collect information on fentanyl use
    - The National Household Survey on Drug Use and Health also does not collect data on fentanyl use at this time.
- The sponsor should consider using monitoring media surveillance, Key Informant Network, and Law enforcement Drug Diversion Units as part of the pharmacovigilance plan.

6.5.6 Other Surveillance Activities

- Recommend evaluating drug use trends in the following manner:
    - Use of sales and prescription data to monitor for disproportionate increases by geographic area
    - The Sponsor plans to educate practitioners on how to deal with patients who may be doctor shopping; please provide details of how doctor shoppers would be identified.
- Recommend a 24-hour toll-free telephone number to provide medical information, receive adverse event information and address product complaints.

Appendix 1

- We request that the sponsor provide additional details and/or clarification on the following topics:
    - Clarify what are the "25 Pain Centers of Excellence", and how they will contribute to the dissemination of educational information
    - Clarify whether educational materials targeted to health care professionals will convey the importance of counseling / educating patients on the appropriate and safe use of the product.
    - Clarify what is meant by "support independent continuing medical education".
    - Clarify how patients will learn that Cephalon accepts returns for the disposal of unwanted drug (to minimize availability of excess product). For example, will this information be included in the Medication Guide?
    - Describe more fully what the "PharmAlert" tool for pharmacists consists of and how it will be distributed.
    - Provide a description of how speakers will be chosen and how they will be trained.
    - Please describe the method(s) planned for returning drug product to Cephalon (ex. Prepaid special mailer provided to patients/hospitals upon request, etc.) and ensuring that diversion will be minimized during the return process.

ODS Fentanyl Buccal Tablets RiskMAP Review Team

Gita Akhavan-Toyserkani, Pharm.D., Safety Evaluator, DDRE
Kristina C. Arnwine, PharmD, Safety Evaluator, DMETS
Jeanine Best, MSN, RN, PNP, Patient Product Information Specialist, DSRCS
Nancy Clark, Pharm.D., Project Manager, DSRCS
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Cathy Dormitzer, Ph.D., Epidemiologist, DDRE
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Lauren Lee, Pharm.D., Safety Evaluator Team Leader, DDRE
Claudia Karwoski, PharmD, Scientific Coordinator, ODS IO
Toni Piazza-Hepp, Pharm.D., Deputy Director, DSRCS
Denise Toyer, PharmD, Deputy Director, DMETS
Mary Willy, Ph.D., Epidemiology Team Leader, DDRE

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/s/

Nancy Clark
4/21/2006 09:24:36 AM
CSO

Gerald DalPan
4/27/2006 11:39:46 AM
MEDICAL OFFICER

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, February 22, 2006 11:45 AM
To: 'Levin, Penny'
Cc: Marchione, Carol; Compton, Kimberly
Subject: Another request for N 21-947

Hi Penny and Carol,

Our medical officer has another request on OVF:

> We request ALL available clinical information (Admitting History and Physical, Discharge Summary, office notes, etc.) for the following four patients from study 3040 **as soon as possible**: 025015, 031016, 034037, 017008.
>
> In three of the cases, the CRF says that more info (such as an Admitting H&P and/or Discharge Summary) is available. However we cannot locate it in the CRF. Patient 017008 was an AE ("allergic reaction") so more info may or may not be available. Please either provide the information or let us know where it can be found in the submission if it is already available.
>
> We need these four right away, but please send the supplementary documentation for all other patients where there is additional information available per the CRF when it is available.

Please let me know when you think you can provide this info and if any clarification of the request is needed.

Thanks,
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
New Phone # as of October 3, 2005 -- 301-796-1191

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/s/

Kimberly Compton
2/22/2006 11:51:44 AM
CSO

From: Compton, Kimberly
Sent: Tuesday, April 18, 2006 7:42 PM
To: 'Levin, Penny'; Marchione, Carol
Subject: proposed tradename

Hi Penny and Carol,

I only have a moment before I need to leave, and I am sorry to be so brief, but I was buried when I came back to the office Monday and have trying to dig out.

Carol, I know you are waiting on a few Actiq items too, but the main thing I wanted to let you know right now is that I am working to draft a letter for OVF that says ODS found the tradename NOT ACCEPTABLE. Our letter will go into the problems they had with it, but I thought I would let you know their decision right away.

I knew you would want to know ASAP as you have been waiting a while for their determination. Will get the letter to you as soon as I can, but in the meantime, we have yet another request:

> Please calculate descriptive statistics for visit 2 (start of titration phase) and visit 3 (end of titration phase/start of double-blind phase) similar to the analysis of vital signs conducted to generate Summary Tables 6.1.1 and 6.2.1 (pages 435 to 440) in the Summary of Clinical Safety (4 Month Safety Update) which compared visits 1 (screening) and 4 (end of study).

Thanks,
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191

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/s/

Kimberly Compton
4/25/2006 03:55:58 PM
CSO

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, February 09, 2006 6:49 PM
To: 'Levin, Penny'
Cc: Marchione, Carol
Subject: Requests for N 21-947

Hi Penny (and Carol),

Our Medical officer has the following requests regarding OVF (N 21-947).

1. The patient diary form indicates that there is a separate "Side Effects Diary" for dosing episodes during which patients experienced one or more side effects. The CRFs (including the completed diaries) submitted do not include this document. Please clarify whether these data were captured as adverse events or indicate where this information is located.

2. Please provide more detail in your analysis of patients with adverse events related to the application site. The description should include a discussion of:

    a. Patients who had symptoms only (i.e. pain, anesthesia, etc.)

    b. Patients who had findings on physical exam (ulcer, vesicles, etc.)

    c. Please provide a narrative and case report forms for the two patients (002001 & 039001) who experienced "residual effects" at the application site.

3. Please provide additional information regarding the specific reason for discontinuation for those patients whose early termination was coded as "consent withdrawn."

21 CFR 10.85(k)

Please let me know if you have any questions on this request or require clarification.

Of course, your prompt response will ensure that our review continue in a timely manner.

Thanks,
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
New Phone # as of October 3, 2005 -- 301-796-1191

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/s/

Kimberly Compton
2/9/2006 06:58:33 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-947 Supplement # Efficacy Supplement Type SE-

Trade Name: TBD
Established Name: Fentanyl citrate effervescent buccal tablets
Strengths: 100, 200, 400, 600 and 800 mcg

Applicant: Cephalon, Inc., c/o Cima Labs
Agent for Applicant: N/A

Date of Application: 8-31-05
Date of Receipt: 8-31-05
Date clock started after UN: N/A
Date of Filing Meeting: 10-12-05
Filing Date: 10-30-05
Action Goal Date (optional): User Fee Goal Date: 6-30-05

Indication(s) requested:

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐

  If yes, explain: According to a search of the Orange Book, N 19-813 for Duragesic (fentanyl transdermal system) has both Pediatric (PED) and New Patient Population (NPP) exclusivity for their product. The PED exclusivity expires 11-20-06 and the NPP expires 5-20-06.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒

  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐

  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐

  If an electronic NDA, all forms and certifications must be in paper and require a signature.

  Which parts of the application were submitted in electronic format? <u>All, except forms and certifications</u>

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐

  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒

  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 65, 447

- End-of-Phase 2 Meeting(s)? Date(s) 12/5/03 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 4/6/05 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☐ YES ☒ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☒ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? **N/A** YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/12/05

BACKGROUND: The referenced product (Actiq, N 20-747) is owned by the same parent company. This applciation is for the same indication as the referenced product, but is a different formulation in that it is an effervescent buccal tablet with no stick, as the referenced product has. The referenced product resides in this review Division.

ATTENDEES: Rigo Roca, Rob Shibuya, Suzanne Thornton-Jones, Dan Mellon, Chandra Chaurasia, Suresh Doddapaneni, Jila Boal, Ravi Harapanhalli, Eric Duffy, Youngman Kim, Kim Compton

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer
Medical:	Rob Shibuya, M.D.
Secondary Medical:	Sharon Hertz, M.D.
Statistical:	Youngman Kim, Ph.D.
Pharmacology:	Suzanne Thornton-Jones, Ph.D.
Statistical Pharmacology:	n/a
Chemistry:	Jila Boal, Ph.D.
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Chandra Chaurasia, Ph.D.
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	CarolAnne Currier
Regulatory Project Management:	Kim Compton
Other Consults:	CSS, ODS, DDMAC

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☒ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Kim Compton, Finalized 11-2-05
Regulatory Project Manager, HFD-170

Concurred by Sara Stradley, CPMS 11-3-05

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   *If "**No,**" skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Actiq, N 20-747

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No,**" skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes,**" skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No,**" please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No,**" skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in the dosage form form a lozenge-on-a-stick to an effervescent buccal tablet.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☒ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☒***

***But the application is submitted by the same sponsor as the referenced drug, so their would be no violation of patent protection since they would hold both patents.

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): The applicant did not request exclusivity.

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☒ NO ☐

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

/s/

Kimberly Compton
11/3/2005 02:04:53 PM
CSO

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

CEPHALON INC
Penny Levin
41 Moores Road PO Box 4011
Frazer PA 19355
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-947

2. TELEPHONE NUMBER
610-7386742

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
(fentanyl efferevescent buccal tablet)

6. USER FEE I.D. NUMBER
PD3006142

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Penny S. Levin	Associate Director Regulatory Affairs	7/12/05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$672,000.00

Form FDA 3397 (12/03)

E

2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

✓ Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65, 447

CIMA labs, Inc.
C/O Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

Attention: Carol Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on April 6, 2005. The purpose of the meeting was to discuss issues related to the finalization of your NDA for your OraVescent fentanyl citrate product in preparation for filing.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: April 6, 2005
Location: Parklawn Building, Conference Room K
Sponsor: CIMA LABS, Inc., a Subsidiary of Cephalon, Inc.
IND: 65, 447
Drug Name: OraVescent fentanyl citrate tablets
Type of Meeting: Type B, Pre-NDA Meeting
Meeting Chair: Bob Rappaport, M.D.
Division of Anesthetic, Critical Care and Addiction Drug Products
Minutes Recorder: Kimberly Compton, Regulatory Project Manager

Industry-Cephalon, Inc. Representatives	
Jonathan Berman, Ph.D.	Sr. Director, Process Technology
Mona Darwish, Ph.D.	Clinical Pharmacology
Ken Fiorelli, Ph.D.	Vice-President, Global Process Development
James Klancke	Sr. Director, Analytical Development
Lilliam Kingsbury, Ph.D.	Vice-President, Biometrics
Carol Marchione	Sr. Director, Regulatory Affairs
John Messina, PharmD.	Director, Clinical Research
Derek Moe, Ph.D.	Sr. Director, Product Development
Gwendolyn Niebler, D.O.,	Sr. Director, Clinical Research
Victor Raczckowski, M.D.	Worldwide Vice-President, Regulatory Affairs
Phillip Simonson, Ph.D.	Sr. Director, Regulatory Affairs
Serge Stankovic, M.D.	Vice-President, Clinical Research
Lothar Tremmel, Ph.D.	Sr. Director, Biometrics
FDA HFD-170	**Title**
Bob Rappaport, M.D.	Division Director
Howard Josefberg, M.D.	Medical Officer
Pat Maturu, Ph.D.	Chemist
Ravi Harapanhalli, Ph.D.	Chemistry Team Leader
Eric Duffy, Ph.D.	Director, Division of New Drug Chemistry II
Suzanne Thornton-Jones, Ph.D.	Pharmacology/Toxicology Reviewer
Dan Mellon, Ph.D.	Supervisory Pharmacologist
David Lee, Ph.D.	Biopharmaceutical Reviewer
Tom Permutt, Ph.D.	Statistical Team Leader
Silvia Calderon, Ph.D.	Controlled Substances Staff
Lanh Green, Pharm.D., M.P.H.	Team Leader, Office of Drug Safety, DDRE
Kim Compton	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss issues related to the finalization of the sponsor's NDA for their OraVescent fentanyl (OVF) citrate product in preparation for filing.

General Discussion:
The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

Opening Comments (Presented at the meeting)

- The meeting package does not make clear:
  - What indication will be sought initially
  - What type of application is planned
    - The table on page 72 states that studies 099-15 and 3040 "will be
  - Which studies will be included in the initial application.
  - How many patients will have completed each study, at the time of database lock
- Our responses assume that you intend to submit a 505(b)2 application for OVF, for the treatment of breakthrough pain in opioid tolerant cancer patients
- Several of the questions requested concurrence that can only be given after the NDA data have been reviewed

Discussion of Opening Comments

The sponsor stated that initially they plan to propose an indication for this product. They will submit the application for this product as a 505(b)(2), with Actiq as the reference product. The sponsor also stated that their anticipated total number of patients was not yet final.

Question 8.3

In the HOW SUPPLIED section of the ACTIQ package insert, it is recommended that only 6 units for each dose strength be prescribed during titration. It is our understanding from Anesta (the original owners of the approved NDA) that this is intended to decrease the risk of accidental pediatric exposure by avoiding having large amounts of extra ACTIQ units in the home after a patient has been titrated to higher doses. Because OVF is in tablet formulation the risk of accidental exposure, diversion, or abuse is no greater than that with other potent opioids in tablet formulation. An OraVescent carton will contain 28 tablets. Since a patient may take up to four 100 mcg tablets as a dose, the 28 tablet carton will represent about 7 doses or about a 2 day supply. Does the Agency concur that the HOW SUPPLIED section can omit reference to limiting the amount prescribed during titration?

FDA Response

- Although limitations identical to those for Actiq may not be appropriate; omission of any such statement entirely may not be the only possible solution
  - We hope to have further discussion about this issue
- The Agency does not necessarily agree with your characterization of OraVescent's potential for abuse, diversion and poisoning
  - No tablet formulation of fentanyl, effervescent or otherwise, has yet been approved
  - Actiq's lollipop formulation originated, in part, because of poisoning and overdose concerns
- Your example that a 28-tablet carton would be sufficient for only two days, is incorrect, as
  - If it is anticipated that someone needs 400 μg/dose initially, they should be prescribed the appropriate dosage strength
  - Simultaneous administration of multiple dosage units has not been evaluated. Labeling for use in this manner would require supporting data.

Discussion of Question 8.3
Dr. Josefberg stated that the Agency would not expect OVF labeling to exactly match that of Actiq, but noted that whatever labeling the sponsor does propose, should be supported by an appropriate and strong rationale. He also stated that Cephalon should consider options for limiting the amount of product dispensed during the initial titration period.

The sponsor stated that their question was actually intended to ascertain whether the Agency considers Cephalon's plans for packaging and labeling to be acceptable. The sponsor intends to label OVF so that patients would use the 100-mcg dose, up to four units at a time, during the initial dose titration period. Dr. Josefberg stated that OVF had not been evaluated for use in that manner. The sponsor indicated that they are currently conducting a bioequivalence (BE) study, to determine if simultaneous administration of four 100-mcg dosage units would be pharmacokinetically equivalent to administration of a single 400-mcg dose. The sponsor indicated that they had just submitted a protocol to the Agency.

The sponsor is planning to package four doses on a card. The four-dose per card configuration has already undergone child-resistance and senior-friendly testing. If new packaging in requested, it would require approximately — for the sponsor to repeat the tests on the new packaging. Dr. Duffy stated that the Agency would not require the sponsor to re-do such testing on production packaging, noting that testing of the pilot packaging would be acceptable.

Question 8.4
We have included a copy of the proposed blister label and carton label in this information package. Does the Agency agree that the warnings and information displayed on these packaging components are adequate?

FDA Response
Precise wording for the label and package insert will be considered during review of the complete application.

Discussion of Question 8.4
Dr. Harapanhalli advised the sponsor to ensure that the label contains appropriate information, especially expiration dating, lot information, NDC number, bar code, etc., in addition to the appropriate warnings and other information needed for drugs of this class, to look at how cluttered the items appear, and also to ensure that appropriate prominence is given to the items.

Dr. Rappaport stated that the Office of Drug Safety (ODS) will also review the carton and container labels (including the blisters). It is not feasible to consult them at this point, though, because these labels are considered in the context of the application as a whole. ODS will, however, be consulted as soon as the application is submitted. Any comments stemming from the ODS labeling review will be conveyed to the sponsor as expeditiously as possible.

Dr. Josefberg informed the sponsor that attempts to print the mock carton labels included in the electronically submitted meeting package (which was a PDF file) caused several different PCs to lock-up, or freeze. He advised the sponsor to check over their application package carefully for workability problems.

Question 8.5
The NDA filing will cross-referenced to the ACTIQ NDA 20-747 for preclinical Pharmacology/Toxicology/ADME information which is a 505(b)(2) application to Janssen's NDA for DURAGESIC®. There have been no additional toxicology studies conducted nor have any additional studies been required by the Agency as discussed during the End-of-Phase 2 meeting. Therefore, Cephalon proposes to solely reference the ACTIQ NDA for all required preclinical information for the OVF NDA. Does the Division concur?

FDA Response
This is acceptable for the current indication,

Discussion of Question 8.5
The sponsor stated that they had received a different response to the same question at a meeting on

FDA Response:

- Toxicology data are acceptable to support the proposed indication. Although not required you are encouraged to conduct a fertility/reproduction studies in male rats (Segment I), pre- and postnatal development study (Segment III), and 2-year carcinogenicity studies in two species. Presently there are no data available for fentanyl for these type of studies.

"Discussion of Question 8.5"
". . . The sponsor stated that they understood that carcinogenicity studies were encouraged, but not required. '

Question 8.7
The specifications proposed by CIMA for the control of this drug product are provided. Does the agency agree that the tests and specifications proposed are appropriate and adequate for the control of this drug product?

FDA Response

- Provide an additional non-specific ID test or one specific ID test for fentanyl in the drug product.

- Rationale provided for the removal of the pH measurement specification does not address whether the pH is likely to change with time on storage. Provide adequate pharmaceutical developmental data indicating that the pH will not change with time on storage or provide a specification to monitor it on stability.

- Provide data on the suitability of the container closure system with regard to the that may jeopardize the product pH over stability.

- The stability data seems to indicate that the disintegration time ranged from seconds over a wide range of batches and storage conditions. Provide an acceptance criteria in the product specifications that is reflective of the observed data.

- Provide a test to assure microbial quality of the product or data from the developmental studies to indicate that the formulation does not promote microbial growth over storage through the intended expiration dating period.

- The Agency acknowledges that the firm agreed to assay the components that contribute to the effervescence, namely ! at release and through stability to ensure adequate effervescence, which seems to have direct bearing on enhanced absorption of the drug.

- Provide additional specifications for in the specifications. The stability data indicates that

conditions. Alternatively, provide data from the pharmaceutical development that such controls are not needed in ensuring product quality and performance through the proposed shelf life.

- The synthetic scheme provided in the package indicates that [redacted] in the drug substance, [redacted] are structural alerts for mutagenicity and should be appropriately controlled in the drug substance in a manner similar to the limits on [redacted]. The justification should be based on the extent of exposure to these structural alerts based on the maximum daily dose of the drug product. Alternatively, these impurities may be qualified in in vitro genotoxicity studies (see Pharmacology/ Toxicology comment slide).

- Similarly, the justification for proposed limit of NMT [redacted] % for [redacted] in the drug product should be based on the expected maximum daily dose of the product.
  - For example, the EMEA Draft guidance on genotoxic impurities recommends a total daily intake of not more than 1.5 mcg for such impurities.

- Physically, 100 mcg and 200 mcg tablets are both white, [redacted] tablets and although they will be debossed with strength, it may be hard to distinguish them. Consider additional color differentiation, if possible.

Discussion of Question 8.7
The sponsor stated that the 100 mcg tablet is ½ the weight of the 200 mcg tablet and has a smaller diameter. They also noted that the primary and secondary packaging will use color differentiation to help distinguish between the two strengths, and the tablets will be debossed with a "1" on the 100 mcg tablet and [redacted] on the 200 mcg tablet.

Dr. Harapanhalli stated that the distinguishing features mentioned may be acceptable to the Division, but noted that ODS might have concerns about the two strengths being the same color. Dr. Rappaport stated that if there were some way to color the tablets differently from one another, the sponsor should utilize it. The sponsor noted that they [redacted]

Question 8.9
Does the Division agree that the same requirements agreed to for the addition of the manufacturing site in Eden Prairie can be applied to the manufacturing site in Salt Lake City?

FDA Response
Provide the following additional supporting data:
- Conformance to the approved specifications
- Case C dissolution profile
- A Justification for the LOD of [redacted] as cited on p.25, along with mass balance and response factors.

Discussion of Question 8.9

Dr. Harapanhalli stated that the Case C profile request was referring to pre- and post- site change data, and not requesting a full F2 analysis since the drug is highly soluble over the entire physiological pH range. He said that the purpose for requesting Case C data was to ensure that the product from the new commercial site behaved similarly to the one from the developmental site. He further stated that, per earlier email agreement, no PK data would be required for this manufacturing site change.

Question 8.11

Please confirm that the responses below to the End-of-Phase 2 Meeting Issues for CMC are acceptable.

FDA Response

- Coordinate with in ensuring their DMF adequately documents for the drug substance.
- Tighten the acceptance criteria for the to conform to the , keeping the sample size the same as agreed to before.
- Ensure that samples from special events such as are sampled in addition to d samples.
- Your acceptance specifications for fentanyl citrate drug substance should also include your own testing of critical quality attributes, the

Discussion of Question 8.11

Chemistry Comments (presented at the meeting)

Question 8.13

For biopharmaceutical studies in healthy volunteers, Cephalon will submit study reports, tables, listings, graphs, and electronic versions of CRFs for patients who die, discontinue due to an adverse event, or experience a serious adverse event while on study. Cephalon does not plan to submit datasets for these studies. Is this acceptable to the Agency?

FDA Response

- No. Complete datasets should be submitted for all clinical pharmacology studies intended to support your NDA.

Question 8.14

Study reports for studies using formulations previous to the final one that is the subject of this NDA (studies 099-06, 099-07, 099-08, 099-09 and 099-10) and studies using vehicle only (studies 099-12 and 099-13) will be included in the NDA. Electronic versions of CRFs for patients who died, discontinued due to an adverse event, or experienced a serious adverse event will also be submitted. Cephalon does not plan to submit datasets for these studies. Is this acceptable to the Agency?

FDA Response

See response to Question 8.13

Discussion of Question 8.13 and 8.14

The sponsor stated that they considered studies completed using early product formulations to be only supportive in nature, and that those studies did not add to the safety or efficacy information on the product. Dr. Lee stated that the Division wants to see all of the pharmacokinetic (PK) data for the relevant formulations. The sponsor should explain why they consider the PK data from trials using the early product formulations not to be relevant. Dr. Lee added that the Division will still want to review safety data from all OVF exposures, including those utilizing the developmental product formulations.

The sponsor inquired about how the Division distinguished between PK data and safety data. Dr. Josefberg stated that safety data from the initial PK trials should include information about drug exposure, basic subject demographics and adverse events. Dr. Rappaport stated that the sponsor should also indicate whether or not patients had received naltrexone blockade.

Dr. Rappaport emphasized that the Division wants to see the safety information on all patient exposures to all fentanyl-containing OVF formulations.

Question 8.16

The studies in the following table will be provided in the clinical section in support of safety and efficacy of the OVF NDA. This list includes studies in both cancer and non-cancer patients who are opioid tolerant. Does the Agency concur that these studies are adequate to support the safety and efficacy of OVF for the indication of the management of BTP in cancer patients who are opioid tolerant?

FDA Response

- Concurrence is not possible at this time since protocols for all the studies had not been submitted for review by the time the meeting package was submitted. However, the brief description of Study 099-16 indicates that it may not be adequate
  - Inadequate number of patients
  - Inadequate exposure
- Additional comments will follow after the study protocols have been reviewed

FDA Comment: Safety Database

- As advised at the 12/2003 meeting "The safety data submitted with the initial NDA submission should be adequate to support" your NDA and "should include at least 500 patients" treated with the to-be-marketed product
  - CIMA had not indicated intent to pursue any indication other than for treatment of BTP in opioid tolerant cancer patients, or to study OVF in other patient populations
- OVF toxicity in relatively healthy chronic pain patients would not necessarily be reflective of toxicity in cancer patients requiring this medicine

Discussion of Question 8.16

The sponsor stated that the proposed Study 099-16 in patients with oral mucositis would be a PK/Tolerability study in patients with mucositis and not a pivotal efficacy study. Dr. Josefberg stated that the proposed single-dose study seems to address the Division's concerns about the PK of the product in mucositis patients, but would probably not be adequate to characterize product tolerability. In the study as planned, there would be no exposure in patients with oral mucositis as OVF would be used in actual practice. The bulk of the safety data in patients with mucositis should come from exposure during clinical use of the product, in settings expected to resemble the product's anticipated real-world use. Such data would not have to be gathered in a stand-alone study. Patients with mucositis could be included in one or more of the studies already planned.

Dr. Rappaport stated that if Study 099-16 (the single-dose PK study in mucositis patients) demonstrated no increase in systemic exposure it would be acceptable to enroll patients with moderate to severe mucositis in the other trials as well. The sponsor pointed out that OVF bioavailability was already nearly 100%. The Division acknowledged that the T_{max} of fentanyl would likely be the only PK parameter to differ substantially in patients with mucositis.

The sponsor asked about the feasibility of conducting a study sufficient to enroll an adequate numbers of patients with oral mucositis, as a Post-Marketing Commitment, with the initial label reflecting the lack of safety data in mucositis patients, but to be revised later, when additional data was available. Dr. Rappaport indicated that the Agency would be receptive to such a proposal.

The sponsor stated that they believe that the previously requested exposure of 500 patients should not be required for this product as they consider it to be a reformulation of their marketed product, Actiq. The sponsor further stated that the C_{max} and AUC for OVF are similar to those for Actiq, and since adverse events (AEs) seem to be related to plasma levels of fentanyl, the sponsor expects OVF's overall AE profile to be very similar to that for Actiq; a product for which a great deal of safety information is already available. The sponsor proposed submitting safety information on OVF from 300 patients, along with the information already known about Actiq.

Dr. Rappaport stated that other safety issues besides patients' absolute plasma levels of fentanyl could exist; for instance, aspiration and choking risk were likely to be different between the two products. Likewise, OVF's effervescence might contribute to some toxicity in cancer patients unique to its formulation. Dr. Rappaport indicated that the Division would internally discuss accepting a smaller than requested safety database. The sponsor proposed submitting data on 250 cancer patients and 70 non-cancer patients, for a total of 320 at the time of submission. Dr. Rappaport stated that the Division will review the request and respond.

***POST-MEETING NOTE:
The sponsor's proposal is acceptable.

Question 8.19
The integrated summary of safety will be incorporated into the NDA in the CTD Summary of Clinical Safety. The proposed statistical analysis plan for the summary of safety and table displays are provided below. Does the FDA agree with Cephalon's proposed analyses of safety information and table displays for this NDA?

FDA Response

- Analysis of safety data is largely descriptive in nature
- The tables titles listed on page 94 ('List of Summaries and Listings') would be appropriate, but not all inclusive
  - For instance, there do not appear to be any cumulative dose-by-duration tables
- If you intend to submit an application for the treatment of breakthrough pain in opioid-tolerant cancer patients, then data from other studies, although of interest, will not be considered pivotal for this application.
- The data should be analyzed and presented by indication, and collectively:
  - cancer studies
  - non-cancer studies
  - all studies

Discussion of Question 8.19

Dr. Josefberg stated that the tables listed in the meeting package seemed appropriate, although not necessarily all inclusive for NDA submission. Dr. Josefberg referred the sponsor to the *Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* (http://www.fda.gov/cder/guidance/3580fnl.pdf) (posted 2/18/2005) to determine how to present information necessary for the NDA review. If the sponsor submits a more detailed template of the NDA's anticipated "Integrated Summary of Safety," taking into account information provided in the above guidance, the Division agreed to provide more specific feedback, if warranted. Dr. Rappaport pointed out that such advice would predominantly address issues in broad strokes.

Question 8.20 (c.)
The integrated summary of efficacy will be incorporated into the NDA in the CTD Summary of Clinical Efficacy. The proposed statistical analysis plan for the summary of efficacy, and the statistical analysis plans for the two Phase 3 studies, 099-14 and C25608/3039/BP/US are provided, along with table displays. Does the FDA agree with the following:
c.) the Statistical Analysis Plans for 099-14 and C25608/ 3039/BP/US

FDA Response
- The advice letter sent on March 5 described concerns with randomization and the proposed primary analysis

Regarding the analysis plans for studies 099-15 and 3039

Randomization
- The study reports should explain the randomization method in detail.
- Clarify whether the 18 possible sequences were assigned equal probabilities.

Primary Analysis
- The proposed primary analysis may confound treatment with period effects because the design is not balanced.
- This concern might be addressed by including period effects in the model.
- The most straightforward approach might be a permutation test with respect to the randomization scheme actually used.

Discussion of Question 20 (c.)
The sponsor indicated they had submitted a response to the Divisions March 10, 2005 advice letter. The primary analysis would remain unchanged but would be supported by a permutation test. Dr. Permutt indicated he would review the submission as quickly as possible and let the sponsor know if their proposed plan is acceptable. He did however note that the characterization of one analysis as "primary" in this context is somewhat artificial, in that if the permutation test did not bear out the primary analysis, the latter would no longer be considered primary.

Question 8.22
The Division has communicated that the Risk Management Program (RMP) for OVF be based upon the RMP for ACTIQ. An outline of our proposal is provided with a summary of the information that we are proposing to include. Does the Agency concur with this outline?

The risks of opiates and of fentanyl are well understood by FDA, and the goals of the risk minimization plan for OVF are unlikely to be altered by FDA's review of the data in the OVF submission. Therefore, rather than waiting until the end of the NDA review to begin substantive discussions on Cephalon's proposed OVF risk minimization plan, Cephalon would like to request monthly meetings with FDA, beginning in May 2004, so that agreement can be reached on the

substantive details of the plan well ahead of the agency's PDUFA date for the NDA application. Does the Agency concur with the proposal?
Regulatory Questions

FDA Response

- The Actiq RMP is a reasonable starting point for development of a RiskMAP for OVF

- Whether modifications will be required, based upon differences between ACTIQ and OVF, will be a review issue based upon the risk assessment of OVF as well as the details of the proposed RiskMAP

- We agree that the risks of opiates and of fentanyl as they relate to abuse and diversion are well understood. However, you should consider making the prevention of accidental ingestion of OVF by children an explicit RiskMAP goal

- If there are any additional or new risks, which may be uniquely associated with the use of the OraVescent technology, we suggest these also be defined as goals in the development of any RiskMAP

- Note that sponsors of high dose and extended-release opiates have recently been tasked with the development of enhanced or active surveillance systems that are
  - more frequently than once per year
  - nationally representative for detection of abuse and diversion

- If you would like to engage the Agency in discussion of the RiskMAP, contact should be through the review Division. The Division will ensure that meetings occur with the appropriate frequency, and that all appropriate CDER staff are involved to assist you in developing a RiskMAP

- To maximize the value of RiskMAP discussions, we recommend as a first step, identification and definition of OVF risks, and corresponding RiskMAP goals. This will provide the rationale for, and data underlying, the RiskMAP tools and plans for evaluation

- The Agency requests that all relevant background information be included, along with the questions for discussion, prior to meetings

Discussion of Question 8.22
Dr. Calderon stated that the sponsor will need to address the risk of accidental exposure and pediatric exposure of the product, especially since there is no mechanistic way to stop absorption of the product as with Actiq.

Dr. Rappaport clarified that the application will not be covered under subpart H, but noted that all opioids are being asked to address these issues. A RiskMAP is independent of subpart H approval. Dr. Rappaport noted that the RiskMAP Guidance is broad and noted that if the sponsor addresses the issues the Division and CSS outlined and follows the Actiq RMP closely, the RiskMAP for this product should be in acceptable. He stated that features and key elements of the plan are more

important than following the format proposed in the Guidance. He instructed the sponsor to assemble their best effort and stated that the Division will then work with the sponsor during the course of the review of the NDA, offering feedback as early as it is available.

Dr. Rappaport stated that the Division is concerned about the period of time the product is in the mouth, pointing out that a patient could conceivably fall asleep with the product in the mouth and then aspirate it, etc. The sponsor should examine their AE data then address this issue (i.e., how much of the product is left at what time point, etc.)

Dr. Calderon pointed out that the tablet is friable and noted that the sponsor should address if it could easily crumble to produce a powder. She requested that the sponsor provide any information they had on exposure to the powder form of the tablet to the Agency.

Dr. Rappaport stated that the product is at the high-risk end of the spectrum, and suggested the sponsor examine the RMP for Palladone as a recently approved product with similar risk. He stated the sponsor could obtain the plan by checking with the sponsor of Palladone, or see parts of the plan in the minutes of the Advisory Committee in which it was discussed.

The sponsor summarized their understanding of the meeting as follows:

- The Division will determine if a prescribing maximum is needed.
- ODS will review the carton and container labeling (including blister labels) as well as the Division, so a commitment cannot be made at this time to the acceptability of the text on the blister as proposed in the meeting package, but the Division is sensitive to the amount of space on the blister and the time the sponsor would need to make changes.
- The sponsor will look into adding color/shading to distinguish the 100 and 200 mcg tablets and propose the change as a post-approval change. The Agency offered to reach agreement on stability requirements to allow the change to be implemented as quickly as possible.
- The Agency understands that an F2 analysis cannot be conducted but that the dissolution data in multiple media would be submitted in support of site changes.
- The [redacted] are considered safety issues since this is a low-dose, high-potency product, so tighter acceptance criteria are requested by the Agency.
- The sponsor will provide appropriate justification why [redacted] The sponsor will provide justification for the tests they propose to ensure no [redacted] during manufacture.
- The sponsor will submit a Pharmaceutical Development Report on [redacted] The sponsor will choose the appropriate test for assessing [redacted]
- The sponsor will submit safety data for non-relevant studies on the product and an explanation of why they feel the studies are not-relevant. For relevant studies, all data are needed.

FDA Response

- You propose to substitute the words 'healthcare practitioners' for 'oncologists and pain specialists' in:

  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.

- This represents a substantial change, with implications for the entire Risk Management Plan

- Precise label wording will be considered during review of the complete application, but

- This substitution would likely not be acceptable for a "treatment of breakthrough cancer pain" type indication

Question 8.2

The appearance of OVF is that of a tablet and has no remarkable features that would be particularly attractive to children as ACTIQ was thought to be since ACTIQ is a lozenge on a handle. If we use the ACTIQ package insert as a template for the OVF package insert, it is our intention to

Does the Agency concur?

FDA Response

- Inapplicable instructions should not be included, but
- Appropriate disposal information for unused doses is still expected
- Again, concurrence with the proposed wording for the package insert will occur after review of the NDA

Nonclinical Comments (Presented on a slide provided prior to the meeting)

- There are structural alerts for mutagenicity that could be present in the drug substance . These impurities require specifications to assure safety. Consult with your DMF holder to decrease the limit of these impurities.
- Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:

  - Minimal genetic toxicology screen (two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - Repeat dose toxicology of appropriate duration to support the proposed indication.

- Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT µg/day (whichever is lower) or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

General Comments (Presented on a slide provided prior to the meeting)
505(b)(2) Applications-

- The following reference is available on the CDER website: October 1999 *DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2)*
- For a 505(b)(2) application you must include the following:
  - Clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.
- A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.
- A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).
- For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)
  - Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.
  - You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any).
- Before submitting your NDA, the guidance recommends that you submit a plan to the reviewing Division that specifically identifies the types of bridging studies that will be conducted. You should also identify those components of your application for which you expect to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.
- The review of this plan will be completed as rapidly as possible, taking into consideration the existing workload at the time of the submission. Therefore, the Division encourages you to submit such a plan well in advance of the NDA submission, to provide adequate time for the review team to evaluate the proposal and resolve any potential concerns that may result in a filing issue or delay in the review process.

Question 8.6
Does the Agency agree with the rationale for the proposed dissolution specification for OVF submitted on 29 August 2003 in Serial No. 003?

FDA Response

- The justification provided for a single point dissolution specification versus a two point specification appears to address many concerns expressed earlier.
- The proposed dissolution specification will be evaluated during the NDA review based on the following criteria:
  - Multi-point dissolution profiles for all clinically relevant batches
  - The manner in which the product is to be used

- The relevance of instructions for use statement such as " to dissolution.
- The actual clinical experience of the patients with regard to the time required for the disappearance of the tablet.
- Potential for swallowing in the event the dissolution is slowed down
- Extent of assurance of intra-tablet homogeneity and its significance on PK/PD.

- The Agency acknowledges that Cephalon will continue to gather multi-point dissolution data for the NDA.

Question 8.8
Does the Agency concur that the SUPAC-IR regulations govern this change to OVF tablets and has Cephalon's correctly applied this guidance to our strategy for the change to debossing and manufacturing locations?

FDA Response
- OVF tablets are considered immediate-release (IR) solid oral dosage forms.
- SUPAC-IR guidance is relevant for post-approval changes following commercial manufacturing campaigns and hence may not be applicable for a pre-approval changes without additional considerations.
- However, principles outlined in the guidance may be used in supporting pre-approval changes with adequate supporting data for OVF tablets based on product and process design.
- Given the complex nature of the formulation, a case C dissolution profile should be provided to support the proposed change without a need for bioequivalence studies.

Question 8.10
Please confirm that OVF tablets can be considered an immediate release (IR) solid, oral dosage form for the purposes of post-approval change assessment. Can the FDA Guidance for Industry pertaining to post approval changes for IR solid, oral dosage forms be applied to this product?

FDA Response
- This is considered an immediate-release solid oral dosage form with some restrictions.
- OVF tablet is not a customary IR tablet since it's performance is based on effervescence and it and is packaged in a foil-foil pouch. Therefore, additional product-specific issues related to the product quality and intended use of the product may be evaluated in assessing the post-approval changes.

- Principles of SUPAC IR and the guidance on changes to approved NDAs (2004) may be applied.

Chemistry Comments (Presented on a slide provided prior to the meeting)
Issues on Manufacturing Science
- A detailed pharmaceutical development plan should be provided documenting how the process and product attributes were optimized and how critical quality attributes were identified.

NDA Stability Data

- In addition to the primary stability data listed in Table 10, provide the following:
  - 6 months accelerated storage stability data for lots
  - Stability updates for both the long term and accelerated storage (6 months) conditions for batches
  - Accelerated storage stability data for the supportive stability batches listed in table 11.
- Stability updates may be submitted no later than the last three months of the review period.
- Statistical analysis of all stability-indicating critical quality attributes should be provided.

Question 8.12

The studies in the table below will be provided in the Clinical Biopharmaceutics/Clinical Pharmacology Sections of the NDA. In addition, other relevant studies involving fentanyl will be referenced in support of this application. Does the Agency concur that data from studies listed are adequate for this section of the NDA?

FDA Response

The clinical pharmacology studies outlined in the meeting package should be adequate, barring unexpected findings.

Question 8.15

Since the End of Phase 2 meeting, Cephalon has decided to conduct Study C25608/3039/BP/US which is similar in design to the 099-14 trial which was discussed during the End of Phase 2 Meeting. The purpose of this new trial is to better characterize the efficacy profile of OVF. Therefore, additional assessments are being conducted, including pain intensity at earlier time points (5 and 10 minutes after administration), and time to meaningful pain relief.

FDA Response

Question 8.17
In the minutes from the pre-IND meeting the Division has asked that at least one half of the patient exposures to OVF be at the upper end of the proposed dose range (— mcg) in order to justify the need for the higher dose strengths. Based upon our initial review of the data from the OVF study 099-14 as well as our experience with ACTIQ, we anticipate that approximately 30%-40% of patients will require doses of fentanyl at this end of the range. If the proportion of subjects treated with higher dose strengths of OVF (—) is similar to the proportion of patients requiring the 1200 and 1600 mcg doses of ACTIQ during the clinical trials with ACTIQ (i.e. 30%-40%), would the FDA agree that there is a need for higher doses of OVF and the proportion expected is adequate?
Clinical Questions

FDA Response

- This recommendation was made (at the EOP2 meeting) because safety data adequate to support approval are required for each dose proposed (100, 200, 400, —
- Data from patient exposure at a 'higher' dose can support the safety of lower doses, but data from lower dose exposure will not support the safety of higher doses
  - Data from a patient treated with the — dose can provide evidence supporting the safety of the 100, 200 and 400 µg doses
  - Data from patients treated at 100, 200, 400 µg will not support the safety of the — dose
- In response to CIMA's inquiry about the consequences of being unable to achieve adequate enrollment at the 'high' doses, the Division stated that 'justification' for such doses might be required
  - The need for an — dose would be in question if very few patients actually titrate themselves up to —
- You should continue to aim for the dose distribution discussed at the EOP2 meeting, but
  - The actual number of patients exposed at the highest, or higher, doses is also important
- Treating 30% of 1500 patients at — would provide more safety data about the — dose, than treating 50% of 500 patients at — would, other things equal
- CIMA anticipated treating at least 500 patients, in clinical settings, with the to-be-marketed OVF formulation

Question 8.18
Since OVF will not be the first marketed oral transmucosal fentanyl product, it is anticipated that some patients taking ACTIQ will be switched to the newer product. Cephalon believes it is important for prescribes to understand how to safely switch patients from ACTIQ to OVF without requiring these patients to undergo an overly burdensome titration. The pharmacokinetic characteristics of 810 mcg OVF dose were shown to be comparable with 1600 mcg of ACTIQ. Based on this finding, a switching paradigm for patients receiving ACTIQ has been designed in studies 099-15 and 3039.

FDA Response

Stable Actiq Dose	Initial OraVescent Dose
200, 400, 600	100
800	200
1200	400
1600	600

- The Actiq to OraVescent conversion proposed is acceptable for open-label dose titration during clinical studies 099-15 and 3039
-

Question 8.20 (a.)
The integrated summary of efficacy will be incorporated into the NDA in the CTD Summary of Clinical Efficacy. The proposed statistical analysis plan for the summary of efficacy, and the statistical analysis plans for the two Phase 3 studies, 099-14 and C25608/3039/BP/US are provided, along with table displays. Does the FDA agree with the following:
a.) the plan to integrate data across the studies in the Summary of Clinical Efficacy

FDA Response

- The individual study reports are of primary interest
  - The NDA should contain one individual, complete study report for each Phase 2/3 trial

Question 8.20 (b.)
The integrated summary of efficacy will be incorporated into the NDA in the CTD Summary of Clinical Efficacy. The proposed statistical analysis plan for the summary of efficacy, and the statistical analysis plans for the two Phase 3 studies, 099-14 and C25608/3039/BP/US are provided, along with table displays. Does the FDA agree with the following:
b.) the proposed analytical methods and table displays in the Summary of Clinical Efficacy

FDA Response

- The table titles listed appear to be appropriate
  - However, no efficacy tables were included
- Each Phase 2/3 efficacy trial report should be accompanied by its corresponding datasets

Question 8.21

Cephalon would like to request a deferral of pediatric commitments [S.650-2(3)]. Does the Agency concur?

FDA Response

As documented on page 11 of the minutes from the EOP2 meeting, the Division will support a deferral until more is known about the product and its potential utility in the treatment of pediatric cancer patients.

ODS Comments (Presented on a slide provided prior to the meeting)

- You are encouraged to review the most recent publicly available information on CDER's views on RiskMAPs; please refer to the Guidance for Industry: Development and Use of Risk Minimization Action Plans and the Guidance for Industry:Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at http://www.fda.gov/cder/guidance/6358fnl.htm and http://www.fda.gov/cder/guidance/6359OCC.htm
- If there is any information on product medication errors from pre-marketing clinical experience, ODS requests that this information be submitted with the NDA application.
- You are encouraged to submit the proprietary name and all associated labels to ODS as soon as available.

Question 8.23

Cephalon is planning on submitting the sNDA in electronic format. The application will be prepared according to CTD format and adapted to the NDA electronic submission format (hybrid submission). Please see the proposal outlined below. Will the FDA accept the proposed overall organization and format of the submission?

FDA Response

- Your application will not be a supplemental NDA
- The overall structure proposed should be acceptable

  "Cephalon is planning on submitting the sNDA in electronic format. The application will be prepared according to CTD format and adapted to the NDA electronic submission format. The submission will consist of CTD documents and Module TOCs placed in the eNDA defined folder structure ... will follow FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format – NDAs" January 1999"

- Each individual study report should include a safety section
- These reports should hyperlink to relevant CRFs

"Patient data listings will be included with the individual clinical study reports. However, individual case report forms will be provided separately, not appended to the individual clinical study reports."

- Data should be organized and presented by clinical study, except in the integrated summary of safety (ISS)

- Dataset definition tables should include, for each field, a list of (for categorical) or range of (for numerical) acceptable values.
  - This information can be included in the "Comments" column.

- Provide hyperlinks from the clinical table of contents, the tabular listing of clinical studies, and each dataset definition table, to the corresponding dataset folders
- Integrated Summary of Safety composite datasets should be provided in an 'ISS' folder
  - All AEs, all TEAEs, all SAEs, etc.
  - One record, or data line, per event
- Key ISS tables should hyperlink to the relevant CRFs
  - Deaths, TESAEs, discontinuations due to SAEs, etc.
- We strongly encourage you to contact the electronic submissions group (esub@cder.fda.gov) for additional assistance with technical aspects of the application.
- We recommend a meeting to demonstrate the electronic submission for the primary reviewers.
- Ideally, this would occur once the NDA is complete and ready for review, but prior to application
- Clarifications, and if necessary, corrections, should be made before the " review clock" starts

For additional information please refer to:

Guidance for Industry: Providing Regulatory Submissions in Electronic Format –General Considerations (http://www.fda.gov/cder/guidance/2867fnl.pdf)

Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDA (http://www.fda.gov/cder/guidance/2353fnl.pdf)

Minutes prepared by: Kim Compton
Minutes concurred by Chair: Bob Rappaport, M.D.

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

/s/

Kimberly Compton
5/5/05 02:02:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65, 447

CIMA Labs, Inc.
10, 000 Valley View Rd.
Eden Prairie, MN 55344

Attention: Philip Simonson, Ph.D.
Director, Regulatory Affairs

Dear Dr. Simonson:

Please refer to the EOP2 meeting between representatives of your firm and FDA on December 5, 2003. The purpose of the meeting was to discuss issues related to the final development phases of your OraVescent fentanyl citrate product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: December 5, 2003

Location: Parklawn Building, Potomac Conference Room

Sponsor: CIMA LABS, Inc.

IND: 65, 447

Drug Name: OraVescent fentanyl citrate tablets

Type of Meeting: Type B, EOP2 Meeting

Meeting Chair: Sharon Hertz, M.D.
Division of Anesthetic, Critical Care and Addiction Drug Products

Minutes Recorder: Kimberly Compton, Regulatory Project Manager

Industry	
CIMA LABS Representatives	
John Hontz, Ph.D.	Chief Operating Officer
Lois Rongstad	Project Manager
	Consultant Medical Officer
	Regulatory Affairs Consultant
	Consultant Statistician,
Jeff Thompson	Senior Director, Project Management

FDA HFD-170	Title
Bob Rappaport, M.D.	Division Director
Celia Winchell, M.D.	Acting Deputy Division Director
Howard Josefberg, M.D.	Medical Officer
Sharon Hertz, M.D.	Pain Team Leader
Pat Maturu, Ph.D.	Chemist
Ravi Harapanhalli, Ph.D.	Acting Chemistry Team Leader
Dan Mellon, Ph.D	Supervisory Pharmacologist
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutical Reviewer
Katherine Bonson, Ph.D.	CSS Staff
Martin Pollock, Pharm.D.	ODS Safety Evaluator
Lahn Green, Pharm. D., M.P.H.	ODS Team Leader
Dionne Price, Ph.D.	Statistics Reviewer
Jo Wyeth	ODS Safety Evaluator
Kim Compton	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss issues related to the final development phases of your OraVescent fentanyl citrate product.

Opening Discussion: Dr. Hertz opened the meeting by observing that the sponsor's product was similar to the Actiq product and that therefore the Agency's concerns would be similar to those surrounding Actiq, if not more so, regarding off-label use, high doses of fentanyl, etc. She stated that there were substantial safety concerns that were brought up with the sponsor previously and have not yet been fully addressed.

General Discussion:
The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

CMC Comments (presented at the meeting)
Fentanyl Citrate Impurities:

- ICH Q3A and Q3B(R) should be followed in setting specifications for individual impurities and degradation products.

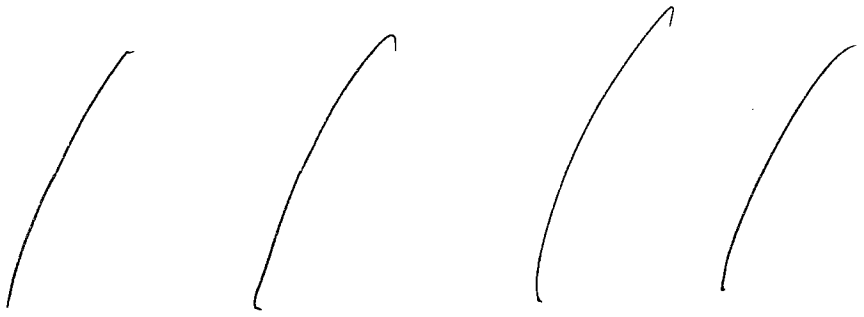
- [redacted] impurity in fentanyl citrate, is a structural alert for mutagenicity, [redacted]. Therefore, limit this impurity to [redacted] n the drug substance or provide the following genotoxic safety qualification.

Genotoxic Qualification of Structural Alerts of Mutagenicity:

- Two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity tested up to the limit dose for each assay.

- Should this qualification produce positive results, the impurity specification should be set < [redacted] Alternatively, the impurity may be assessed for carcinogenic potential in either a standard 2-year bioassay or an alternative transgenic mouse model.

Fentanyl Citrate - Physical Attributes:



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✓ Trade Secret / Confidential

Draft Labeling

Deliberative Process

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Discussion of CMC Comments

The sponsor asked for clarification of the need for the genotoxic qualification of the impurity. The Division confirmed that the genetic toxicology studies would only have to be completed if the levels of the impurity cannot be decreased below the specified threshold. Specifically, Dr. Mellon stated that the sponsor should set specifications for this impurity regardless of the final levels obtained to insure consistent batches. He noted that it was not clear from the package if they were currently set low enough and requested that the sponsor clarify this point.

Dr. Harapanhalli stated that the sponsor should ensure the drug substance is consistent. He also commented, regarding the
that these recommendations were modeled after the USP. He also recommended that the applicant reference
If the sponsor chooses to perform them differently, they will need to provide a justification and explanation along with appropriate supporting data to the Agency. The sponsor stated that they will take this information to their CMC team.

Question #1

Does the Division agree that the Cmax of the 1600 mcg Actiq unit is the appropriate pharmacokinetic parameter to reference in the identification of the highest OraVescent fentanyl citrate dose?

FDA Response

- Both C_{max} and AUC have been reported to correlate with clinical endpoints for opioids. To identify an OraVescent dose strength comparable to a particular Actiq dose strength for use in pivotal trials, then comparability should be demonstrated on both C_{max} and AUC.

- Dose proportionality is critical to safe use of this product

- We have concerns about the selection of a dose comparable to the 1600 μg dose of Actiq

Discussion of Question 1

The sponsor stated that the C_{max} seemed more important to the safety of the dose than the AUC. They stated that the AUC wouldn't meet strict bioequivalence standards, but noted that they would not want to be approved based on that aspect of the product, rather that it was to be used to help determine if the appropriate safety information in the literature is available. Dr. Al-Fayoumi stated that if the sponsor is looking for acute safety, the C_{max} might be the right characteristic, but noted that the AUC cannot be ignored, especially for the longer term safety.

- The Division made this point at your pre-IND meeting

Discussion of Clinical Comments
Dr. Hertz stated that enough patients in the Actiq program interrupted doses such that Actiq's sponsor had to develop an interim storage solution as part of their development plan indicating that not all patients will need the total dose of this product each time they use it. The Agency has adverse events from many patients using Actiq and despite the best efforts, the product is used off-label. The sponsor stated that the *in vivo* dwell time is approximately 18 – 20 minutes in the human mouth. The product has some integrity while dwelling, so a patient could spit it out. The sponsor stated that they would develop a tablet that will deliver no more fentanyl than the 200 mcg Actiq delivers. The sponsor stated that they suggested removing the high and low doses at the pre-IND meeting, but that the Agency was against removal of the low dose and they will pursue development of a dose comparable to 200 mcg.

Question #3

Does the Division agree that the proposed Phase III efficacy trial (protocol 099-14), which would be initiated following the dose proportionality study utilizing a mITT population as the primary analysis population, will adequately support the registration of OraVescent fentanyl citrate tablets as a single pivotal study?

FDA Response

- Overall, yes
- The initial OraVescent dose (during titration) should be administered in a monitored setting
- In order to improve compliance (reduce missing entries) and encourage timely ratings (reduce back-filling) you might consider supplying timers with audible reminders along with the patient diaries

Discussion of Question 3
Dr. Hertz stated that the initial dose of OraVescent should be administered in a monitored setting even for fentanyl tolerant patients.

Question # 4

Does the Division agree on the size of the proposed safety database? Furthermore, does the Division agree with the proposal to submit interim safety data (with complete efficacy data) at the time of submission and follow up safety data 4 months post NDA submission?

FDA Response

- The safety database should include at least 500 patients treated with the formulation that you intend to market
- At least half of these should have received the highest dose that you intend to market, for the expected duration of use

- Most subjects studied to date received single 200 μg doses of early formulations, and/or naltrexone blockade

- Naltrexone blocked subjects will not be included in the total number of exposures

- In order to provide an adequately sized, and more representative safety database you may wish to consider enrolling patients directly into an open-label study

- The safety data submitted with the initial NDA submission should be adequate to support the requirements, with any additional new data submitted with the 120-day update.

Discussion of Question 4

The sponsor stated that the first 3 studies were done without NTX blocking. NTX was used based on the Agency's suggestion. Dr. Hertz clarified that the Agency indicated that naltrexone was necessary for the safety of normal volunteers receiving 600 mcg of fentanyl and greater. Dr. Hertz also stated that since the sponsor is proposing a large dose range, and since there is very high bioavailiability for the product, safety data from a large number of patients at higher doses is needed. The Division has concerns regarding the safety of these high dose fentanyl products and has requested similar data from sponsors with similar products. Dr. Hertz stated that the sponsor could prepare an argument for the Division to review regarding the submission of less data but such arguments would need to be quite compelling. The sponsor inquired if any of the safety concerns would be decreased if they choose a dose comparable to 1200 or 800 mcg fentanyl instead of 1600 mcg. Dr. Hertz requested that the sponsor submit such a plan for the Division to review.

Dr. Hertz stated that the purpose behind the 120-day safety update is to provide updated information, not to serve as a mechanism for submitting required data or a rolling review. The sponsor stated that they anticipate having experience of 1 – 7 months in 75 patients, then 4 months later, about 300-day data in about 90 patients for long-term exposure information, with no new initial exposure data. Dr. Hertz stated that the number of patients proposed seemed acceptable.

Question # 5

Does the Division agree that the mucosal tolerance study in normal volunteers (099-12) will provide an acceptable measure of the local irritation potential of the OraVescent formulation administered buccally?

FDA Response

- The overall design of the study appears to be acceptable

- You have not provided sufficient details about the oral assessments

- The adequacy of the results will depend on the adequacy of the oral assessments

- Before you proceed you may wish to specify how, by whom, and when these examinations will be done

Discussion of Question 5
Dr. Josefberg stated that the sponsor should propose a specific plan and the Division would review it for acceptability.

Question # 6

Does the Division agree that the pharmacokinetic study in patients with active oral mucositis (protocol 099-16), which proposes an abbreviated blood sampling design and limited pharmacokinetic assessments (C_{max} and T_{max}), will provide sufficient labeling guidance for use of OraVescent fentanyl citrate in patients with mucositis?

FDA Response
Yes

Question #7

Is the proposed risk management program suitable for the commercialization of OraVescent fentanyl citrate tablets?

FDA Response

- There are concerns about the safety of this product that will need to be adequately addressed in the RMP.

- How will patients and prescribers be educated to understand the differences between this product and Actiq?

- Will there be any elements of the RMP to help prevent overdose such as packaging or educational material, or suggested limits on dosing?

Discussion of Question 7
Dr. Josefberg stated that the sponsor's RMP is really only an outline and some of the Division's concerns were not addressed. Dr. Hertz stated that we will need to explore the situation and possibilities concerning how this product will be packaged in relation to other C-II products. She also noted that key items from other RMPs included:

- avoiding unintended exposure in non-patients
- methods of surveillance in post-marketing
- adequate education programs
- minimization of off-label use.

Clinical Comments (presented at the meeting)

Risk Management Plan:

- How will off label use be minimized?
- What approaches will be used to reduce the risk of diversion?
- What type of surveillance program will be implemented to detect adverse events, misuse, abuse, and diversion?

Discussion of Clinical Comments
Dr. Bonson stated that the Agency wanted to avoid any situations like that with OxyContin. Because of the rapidity in which this drug enters the body and the high fentanyl dose, the situation is very serious and of major concern to the Agency. Dr. Hertz stated that the sponsor of Actiq had attempted to address some these issues by preparing the interim storage container, and by making available a kit that included a locking pouch and a lock for a cabinet. She noted that the Agency is taking a prospective risk management approach for all high-dose opioids. However, this product is somewhat different from many other opioids and of special concern.

Question #8

CIMA plans to request a waiver of pediatric study requirements for OraVescent fentanyl citrate. Is the Division in agreement that pediatric studies are not appropriate for this product at this time?

FDA Response

Yes, but the Division will support a *deferral* until more is known about the product and potential utility for pediatric cancer patients.

Closing Discussion
Dr. Winchell stated that transcripts and minutes of recent Advisory Committee meetings dealing with RMPs for opioid analgesics are available to the public. The general recommendations from those meetings will be used to develop risk management plans for opioids, with specific features tailored to the risks presented by individual products.

Action Items:
The Agency will prepare the official minutes of the meeting and provide the sponsor with a copy.

Minutes prepared by: Kim Compton
Minutes concurred by Chair: Sharon Hertz, M.D.

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

/s/

Kimberly Compton
3/30/04 12:57:51 PM