CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-449

Name: Fentanyl Transdermal System, 25 mcg/hour, 50 mcg/hour, 75 mcg/hour and 100 mcg/hour

Sponsor: TEVA Pharmaceuticals USA

Approval Date: October 20, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-449

TEVA Pharmaceuticals USA
Attention: Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 17, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fentanyl Transdermal System, 25 mcg/hour, 50 mcg/hour, 75 mcg/hour and 100 mcg/hour.

Reference is also made to your amendments dated May 3, and June 5, 2006; January 16, January 31, April 3, April 26, August 30, and November 28, 2007; and March 14, June 3, June 18, August 26, and September 18, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Fentanyl Transdermal System, 25 mcg/hour, 50 mcg/hour, 75 mcg/hour, and 100 mcg/hour to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Duragesic-25, Duragesic-50, Duragesic-75 and Duragesic-100 Transdermal System, respectively, of Ortho McNeil Janssen.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

In-vitro dissolution testing should be conducted in 500 mL (for the 25 and 50 mcg/hour strengths) and 900 mL (for the 75 and 100 mcg/hour strengths) of phosphate buffer, pH 6.8 at 32°C±0.5°, using USP apparatus 6 (cylinder), at 50 rpm. The test product should meet the following "interim" specifications:

Time (hours)	Percent of Labeled Amount Dissolved
2	(b) (4)
6	
12	
72	

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 77-449***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
10/20/2008 11:11:29 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

LABELING

FENTANYL TRANSDERMAL SYSTEM CII

6900
6901
6902
6903

℞ only

Iss. 7/2008
3001664 Rev. 08/08

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

Fentanyl transdermal system contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (fentanyl transdermal system) may be a particular target for abuse and diversion.

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that:

- **requires continuous, around-the-clock opioid administration for an extended period of time, and**
- **cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids**

Fentanyl transdermal system should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time**
- **in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain (e.g., use on an as needed basis [prn])**

(See CONTRAINDICATIONS for further information.)

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of fentanyl transdermal system with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see CLINICAL PHARMACOLOGY, Drug Interactions; WARNINGS; PRECAUTIONS; and DOSAGE AND ADMINISTRATION for further information).

The safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS, Pediatric Use).

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

Fentanyl transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing fentanyl transdermal system in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

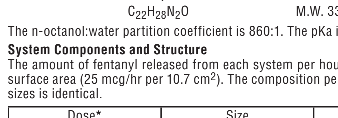
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Fentanyl transdermal systems are intended for transdermal use (on intact skin) only. Do not use a fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way.

Avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing fentanyl transdermal systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the fentanyl transdermal system dose should be adjusted if necessary.

DESCRIPTION

Fentanyl transdermal system is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidyl] propanamide. The structural formula is:



$C_{22}H_{28}N_2O$ M.W. 336.5

The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

System Components and Structure

The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/hr per 10.7 cm^2). The composition per unit area of all system sizes is identical.

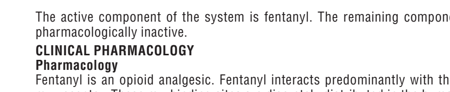
Dose* (mcg/hr)	Size (cm^2)	Fentanyl Content (mg)
25	10.7	2.76
50	21.4	5.52
75	32.1	8.28
100	42.8	11.04

* Nominal delivery rate per hour

Fentanyl transdermal system is a rectangular unit comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1. A BACKING LAYER OF POLYESTER FILM;
2. FENTANYL IN A POLYISOBUTENE ADHESIVE MATRIX THAT CONTROLS THE RATE OF FENTANYL DELIVERY TO THE SKIN SURFACE; AND
3. A PROTECTIVE POLYESTER RELEASE LINER.

Before use, a protective liner covering the adhesive layer is removed and discarded.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system.

In addition to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination. At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in clinical studies indicate that clinically significant histamine release rarely occurs with fentanyl administration. Clinical assays show no clinically significant histamine release in dosages up to 50 mcg/kg.

Pharmacokinetics (see graph and tables)

Fentanyl transdermal system releases fentanyl from the drug matrix at a nearly constant amount per unit time. The concentration gradient existing between the adhesive matrix and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72 hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (25, 50, 75, and 100 mcg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient.

Following fentanyl transdermal system application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial fentanyl transdermal system application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hour application period. Peak serum concentrations of fentanyl generally occurred between 24 and 72 hours after initial application (see **TABLE A**). Serum fentanyl concentrations achieved are proportional to the fentanyl transdermal system delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72 hour applications, patients reach and maintain a steady state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl (see graph and **TABLE B**).

The kinetics of fentanyl in normal subjects following application of a 25 mcg/hr fentanyl transdermal system were bioequivalent with or without a Bioclusive™ overlay (polyurethane film dressing).

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13 to 22) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3 to 12) hours.

Serum Fentanyl Concentrations
Following Multiple Applications of A Fentanyl Transdermal System 100 mcg/hr (n = 10)

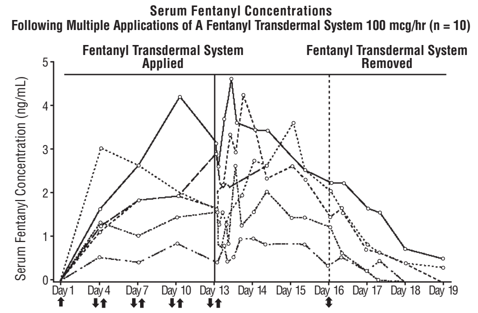


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72 HOUR APPLICATION OF A FENTANYL TRANSDERMAL SYSTEM

	Mean (SD) Time to Maximal Concentration T_{max} (hr)	Mean (SD) Maximal Concentration C_{max} (ng/mL)
Fentanyl Transdermal System 25 mcg/hr	38.1 (18.0)	0.6 (0.3)
Fentanyl Transdermal System 50 mcg/hr	34.8 (15.4)	1.4 (0.5)
Fentanyl Transdermal System 75 mcg/hr	33.5 (14.5)	1.7 (0.7)
Fentanyl Transdermal System 100 mcg/hr	36.8 (15.7)	2.5 (1.2)

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in 17 hours.

TABLE B
RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/hr) Range [70 kg]	Volume of Distribution V_{SS} (L/kg) Range	Half-Life $t_{½}$ (hr) Range
Surgical Patients	27 to 75	3 to 8	3 to 12
Hepatically Impaired Patients	3 to 80 +	0.8 to 8 +	4 to 12 +
Renally Impaired Patients	30 to 78	-	-

+ Estimated

NOTE: Information on volume of distribution and half-life not available for renally impaired patients.

Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood. The average volume of distribution for fentanyl is 6 L/kg (range 3 to 8; N = 8).

Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Special Populations

Hepatic or Renal Disease

Insufficient information exists to make recommendations regarding the use of fentanyl transdermal system in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Pediatric Use

In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to **DOSAGE AND ADMINISTRATION** section.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients (N = 4) indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these fndings to fentanyl transdermal system is unknown at this time.

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients or when opioids are given in conjunction with other agents that depress respiration.

Fentanyl transdermal system should be used with caution in elderly, cachetic or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

The interaction between ritonavir, a CYP3A4 inhibitor, and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52% to 420%) increase in fentanyl $AUC_{0-\infty}$. Coadministration of ritonavir in patients receiving fentanyl transdermal system has not been studied; however, an increase in fentanyl AUC is expected (see **BOX WARNING**, **WARNINGS**, **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore, potential interactions may occur when fentanyl transdermal system is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce CYP3A4 activity may reduce the efficacy of fentanyl transdermal system. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see **BOX WARNING**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** for further information).

Pharmacodynamics

Ventilatory Effects

Because of the risk for serious or life-threatening hypoventilation, fentanyl transdermal system is CONTRAINDICATED in the treatment of post-operative and acute pain and in patients who are not opioid-tolerant. In clinical trials of 357 patients with acute pain treated with fentanyl transdermal system, 13 patients experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In these studies, the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, postmarketing reports have been received that describe opioid-naïve post-operative patients who have experienced clinically significant hypoventilation and death with fentanyl transdermal system.

While most adult and pediatric patients using fentanyl transdermal system chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to fentanyl transdermal system. The use of fentanyl transdermal system is contraindicated in patients who are not tolerant to opioid therapy.

The use of fentanyl transdermal system should be monitored by clinical evaluation, especially within the initial 24 to 72 hours when serum concentrations from the initial patch will peak, and following increases in dosage. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older.

See **BOX WARNING**, **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, **ADVERSE REACTIONS** and **OVERDOSAGE** for additional information on hypoventilation.

Cardiovascular Effects

Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with fentanyl transdermal system was less than 1%.

CNS Effects

Central nervous system effects increase with increasing serum fentanyl concentrations.

INDICATIONS AND USAGE

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

Fentanyl transdermal system should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr (see **DOSAGE AND ADMINISTRATION**). Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could result, fentanyl transdermal system is contraindicated for use on an as needed basis (i.e., prn), for the management of post-operative or acute pain, or in patients who are not opioid-tolerant or who require opioid analgesia for a short period of time (see **BOX WARNING** and **CONTRAINDICATIONS**).

An evaluation of the appropriateness and adequacy of treating with immediate-release opioids is advisable prior to initiating therapy with any modified-release opioid. Prescribers should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids, in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time**
- **in the management of post-operative pain, including use after out-patient or day surgeries, (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain (e.g., use on an as needed basis [prn])**
- **in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment**
- **in patients who have acute or severe bronchial asthma**

Fentanyl transdermal system is contraindicated in patients who have or are suspected of having paralytic ileus.

Fentanyl transdermal system is contraindicated in patients with known hypersensitivity to fentanyl or any components of this product.

WARNINGS

Fentanyl transdermal system is intended for transdermal use (on intact skin) only. Do not use a fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way.

The safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS, Pediatric Use).

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. The mean elimination half-life of fentanyl transdermal system is 17 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after fentanyl transdermal system removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations 17 hours after system removal.

Fentanyl transdermal system should be prescribed only by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.

All patients and their caregivers should be advised to avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. Patients should be advised against taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40ºC (104ºF) due to temperature-dependent increases in fentanyl released from the system and increased skin permeability. **Patients wearing fentanyl transdermal systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the fentanyl transdermal system dose should be adjusted if necessary.**

Death and other serious medical problems have occurred when people were accidentally exposed to fentanyl transdermal system. Examples of accidental exposure include transfer of a fentanyl transdermal system from an adult's body to a child while hugging, accidental sitting on a patch and possible accidental exposure of a caregiver's skin to the medication in the patch while the caregiver was applying or removing the patch.

Placing fentanyl transdermal system in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking or overdose that could result in death.

Misuse, Abuse and Diversion of Opioids

Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing fentanyl transdermal system in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Fentanyl transdermal system has been reported as being abused by other methods and routes of administration. These practices will result in uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Hypoventilation (Respiratory Depression)

Serious or life-threatening hypoventilation may occur at any time during the use of fentanyl transdermal system especially during the initial 24 to 72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the patch is removed, hypoventilation may persist beyond the removal of fentanyl transdermal system. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized.

The use of concomitant CNS active drugs requires special patient care and observation.

Respiratory depression is the chief hazard of opioid agonists, including fentanyl the active ingredient in fentanyl transdermal system. Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

Fentanyl transdermal system should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of fentanyl transdermal system may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Chronic Pulmonary Disease

Because potent opioids can cause serious or life-threatening hypoventilation, fentanyl transdermal system should be administered with caution to patients with preexisting medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

Fentanyl transdermal system should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. Fentanyl transdermal system should be used with caution in patients with brain tumors.

Interactions with other CNS Depressants

The concomitant use of fentanyl transdermal system with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

Interactions with Alcohol and Drugs of Abuse

Fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Interactions with CYP3A4 Inhibitors

The concomitant use of fentanyl transdermal with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and any CYP3A4 inhibitors should be carefully monitored for an extended period of time, and dosage adjustments should be made if warranted (see **BOX WARNING**; **CLINICAL PHARMACOLOGY**, **Drug Interactions**; **PRECAUTIONS**; and **DOSAGE AND ADMINISTRATION** for further information).

PRECAUTIONS

General

Fentanyl transdermal system should not be used to initiate opioid therapy in patients who are not opioid-tolerant. Children converting to fentanyl transdermal system should be opioid-tolerant and 2 years of age or older (see **BOX WARNING**).

Patients, family members, and caregivers should be instructed to keep patches (new and used) out of the reach of children and others for whom fentanyl transdermal system was not prescribed. A considerable amount of active fentanyl remains in fentanyl transdermal system even after use as directed. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that could result in death.

Cardiac Disease

Fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hepatic or Renal Disease

Insufficient information exists to make recommendations regarding the use of fentanyl transdermal system in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Use in Pancreatic/Biliary Tract Disease

Fentanyl transdermal system may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like fentanyl transdermal system may cause increases in the serum amylase concentration.

Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical Dependence

Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION**, **Discontinuation of Fentanyl Transdermal System**).

Ambulatory Patients

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery. Patients who have been given fentanyl transdermal system should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Information for Patients

Patients and their caregivers should be provided with a Medication Guide each time fentanyl transdermal system is dispensed because new information may be available.

Patients receiving fentanyl transdermal systems should be given the following instructions by the physician:

1. Patients should be advised that fentanyl transdermal systems contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.
2. Patients should be advised that each fentanyl transdermal system may be worn continuously for 72 hours, and that each patch should be applied to a different skin site after removal of the previous transdermal patch.
3. Patients should be advised that fentanyl transdermal systems should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. Additionally, patients should be advised of the following:
   - In young children or persons with cognitive impairment, the patch should be put on the upper back to lower the chances that the patch will be removed and placed in the mouth.
   - Hair at the application site should be clipped (not shaved) prior to patch application.
   - If the site of fentanyl transdermal system application must be cleansed prior to application of the patch, do so with clear water.
   - Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics.
   - Allow the skin to dry completely prior to patch application.
4. Patients should be advised that fentanyl transdermal system should be applied immediately upon removal from the sealed blister package and after removal of the protective liner. Additionally the patient should be advised of the following:
   - The fentanyl transdermal system should not be used if the seal is broken, or if the patch is cut, damaged, or changed in any way.
   - The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.
   - The patch should not be folded so that only part of the patch is exposed.
5. Patients should be advised that the dose of fentanyl transdermal system or the number of patches applied to the skin should NEVER be adjusted without the prescribing healthcare professional's instruction.
6. Patients should be advised that while wearing the patch, they should avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources, such as:
   - heating pads,
   - electric blankets,
   - sunbathing,
   - heat or tanning lamps,
   - saunas,
   - hot tubs or hot baths, and
   - heated water beds, etc.
7. Patients should also be advised of a potential for temperature dependent increases in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, patients who develop a high fever or increased body temperature due to strenuous exertion while wearing the patch should contact their physician.
8. Patients should be advised that if they experience problems with adhesion of the fentanyl transdermal system, they may tape the edges of the patch with first aid tape. If problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing (e.g., Bioclusive™).
9. Patients should be advised that if the patch falls off before 72 hours a new patch may be applied to a different skin site.
10. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used fentanyl transdermal systems after removal from the skin.
11. Patients should be instructed that, if the drug matrix accidentally contacts the skin, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of fentanyl to go through the skin.
12. Patients should be advised that fentanyl transdermal system may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
13. Patients should be advised to refrain from any potentially dangerous activity when starting on fentanyl transdermal system or when their dose is being adjusted, until it is established that they have not been adversely affected.
14. Patients should be advised that fentanyl transdermal system should not be combined with alcohol or other CNS depressants (e.g., sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
15. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with fentanyl transdermal system.
16. Patients should be advised of the potential for severe constipation.
17. Patients should be advised that if they have been receiving treatment with fentanyl transdermal system and cessation of therapy is indicated, it may be appropriate to taper fentanyl transdermal system dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
18. Patients should be advised that fentanyl transdermal system contains fentanyl, a drug with high potential for abuse.
19. Patients, family members and caregivers should be advised to protect fentanyl transdermal system from theft or misuse in the work or home environment.
20. Patients should be instructed to keep fentanyl transdermal system in a secure place out of the reach of children due to the high risk of **fatal respiratory depression**.
21. Patients should be advised that fentanyl transdermal system should never be given to anyone other than the individual for whom it was prescribed because of the risk of death or other serious medical problems to that person for whom it was not intended.
22. Patients should be informed that, if the patch dislodges and accidentally sticks to the skin of another person, they should immediately take the patch off, wash the exposed area with water and seek medical attention for the accidentally exposed individual.
23. When fentanyl transdermal system is no longer needed, the unused patches should be removed from their blisters, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.
24. Women of childbearing potential who become, or are planning to become pregnant, should be advised to consult a physician prior to initiating or continuing therapy with fentanyl transdermal system.
25. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.

Drug Interactions

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when fentanyl transdermal system is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce CYP3A4 activity may reduce the efficacy of fentanyl transdermal system. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fasamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause fatal respiratory depression. Patients receiving fentanyl transdermal system and any CYP3A4 inhibitor should be carefully monitored for an extended period of time, and dosage adjustments should be made if warranted (see **BOX WARNING**; **CLINICAL PHARMACOLOGY**, **Drug Interactions**; **WARNINGS**; and **DOSAGE AND ADMINISTRATION** for further information).

Central Nervous System Depressants

The concomitant use of fentanyl transdermal system with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation, or potentially result in coma or death. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

MAO Inhibitors

Fentanyl transdermal system is not recommended for use in patients who have received MAOI within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of fentanyl HCl have not been conducted. There was no evidence of mutagenicity in the Ames *Salmonella* mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration *in-vitro* assays.

The potential effects of fentanyl on male and female fertility were examined in the rat model via two separate experiments. In the male fertility study, male rats were treated with fentanyl (0, 0.025, 0.1, or 0.4 mg/kg/day) via continuous intravenous infusion for 28 days prior to mating; female rats were not treated. In the female fertility study, female rats were treated with fentanyl (0, 0.025, 0.1, or 0.4 mg/kg/day) via continuous intravenous infusion for 14 days prior to mating until day 16 of pregnancy; male rats were not treated. Analysis of fertility parameters in both studies indicated that an intravenous dose of fentanyl up to 0.4 mg/kg/day to either the male or the female alone produced no effects on fertility (this dose is approximately 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In a separate study, a single daily bolus dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the human dose for a period of 12 days.

Pregnancy

Teratogenic Effects

Pregnancy category C

No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In contrast, the intravenous administration of fentanyl (0, 0.01, or 0.03 mg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 3 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fentanyl transdermal system should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

The potential effects of fentanyl on prenatal and postnatal development were examined in the rat model. Female Wistar rats were treated with 0, 0.025, 0.1, or 0.4 mg/kg/day fentanyl via intravenous infusion from day 6 of pregnancy through 3 weeks of lactation. Fentanyl treatment (0.4 mg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at day 4. Both the mid-dose and high-dose fentanyl animals demonstrated alterations in some physical landmarks of development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at day 28 which recovered by day 50). The mid-dose and the high-dose are 0.4 and 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis.

Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, fentanyl transdermal system is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore, fentanyl transdermal system is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

The safety of fentanyl transdermal system was evaluated in three open-label trials in 291 pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/hr and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of fentanyl transdermal system therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials. Approximately 90% of the total daily opioid requirement (fentanyl transdermal system plus rescue medication) was provided by fentanyl transdermal system.

Fentanyl transdermal system was not studied in children under 2 years of age.

Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see **DOSAGE AND ADMINISTRATION** and **BOX WARNING**).

To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl transdermal system (see **DOSAGE AND ADMINISTRATION**) and monitor adhesion of the system closely.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients (N = 4) indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to transdermal fentanyl system is unknown at this time.

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients or when opioids are given in conjunction with other agents that depress respiration.

Fentanyl transdermal system should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

In postmarketing experience, deaths from hypoventilation due to inappropriate use of fentanyl transdermal system have been reported (see **BOX WARNING** and **CONTRAINDICATIONS**).

Premarketing Clinical Trial Experience

Although fentanyl transdermal system use in post-operative or acute pain and in patients who are not opioid-tolerant is CONTRAINDICATED, the safety of fentanyl transdermal system was originally evaluated in 357 post-operative adult patients for 1 to 3 days and 153 cancer patients for a total of 510 patients. The duration of fentanyl transdermal system use varied in cancer patients; 56% of patients used fentanyl transdermal system for over 30 days, 28% continued treatment for more than 4 months, and 10% used fentanyl transdermal system for more than 1 year.

Hypoventilation was the most serious adverse reaction observed in 13 (4%) post-operative patients and in 3 (2%) of the cancer patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naive patients.

Various adverse events were reported; a causal relationship to fentanyl transdermal system was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received fentanyl transdermal system. There has been no attempt to correct for a placebo effect, concomitant use of other opioids, or to subtract the frequencies reported by placebo-treated patients in controlled trials.

Adverse reactions reported in 153 cancer patients at a frequency of 1% or greater are presented in **TABLE 1**; similar reactions were seen in the 357 post-operative patients.

In the pediatric population, the safety of fentanyl transdermal system has been evaluated in 291 patients with chronic pain 2 to 18 years of age. The duration of fentanyl transdermal system use varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16 to 30 days; 16% for 31 to 60 days; and 17% for at least 61 days. Twenty-five patients were treated with fentanyl transdermal system for at least 4 months and 9 patients for more than 9 months.

There was no apparent pediatric-specific risk associated with fentanyl transdermal system use in children as young as 2 years old when used as directed. The most common adverse events were fever (35%), vomiting (33%), and nausea (24%).

Adverse events reported in pediatric patients at a rate of ≥ 1% are presented in **TABLE 1**.

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%)
Adult (N = 380) and Pediatric (N = 291) Clinical Trial Experience

Body System	Adults	Pediatrics
Body as a Whole	Abdominal pain*, headache*, fatigue*, back pain, fever, influenza-like symptoms*, accidental injury, rigors	Pain*, headache*, fever, syncope, abdominal pain, allergic reaction, flushing
Cardiovascular	Arrhythmia, chest pain	Hypertension, tachycardia
Digestive	Nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence	Nausea**, vomiting**, constipation*, dry mouth, diarrhea
Nervous	Somnolence**, insomnia, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction	Somnolence*, nervousness*, insomnia*, asthenia*, hallucinations, anxiety, depression, convulsions, dizziness, tremor, speech disorder, agitation, stupor, confusion, paranoid reaction
Respiratory	Dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis*, hiccups, bronchitis, rhinitis, sinusitis, upper respiratory tract infection*	Dyspnea, respiratory depression, rhinitis, coughing
Skin and Appendages	Sweating**, pruritus*, rash, application site reaction – erythema, papules, itching, edema	Pruritus*, application site reaction*, sweating increased, rash, rash erythematous, skin reaction localized
Urogenital	Urinary retention* Micturition disorder	Urinary retention

* Reactions occurring in 3% to 10% of fentanyl transdermal system patients
** Reactions occurring in 10% or more of fentanyl transdermal system patients

The following adverse effects have been reported in less than 1% of the 510 adult post-operative and cancer patients studied:

Cardiovascular: bradycardia
Digestive: abdominal distention
Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility
Respiratory: stertorous breathing, asthma, respiratory disorder
Skin and Appendages, General: exfoliative dermatitis, pustules
Special Senses: amblyopia
Urogenital: bladder pain, oliguria, urinary frequency

Postmarketing Experience – Adults

The following adverse reactions have been reported in association with the use of fentanyl transdermal system and not reported in the premarketing adverse reactions section above:

Body as a Whole: edema
Cardiovascular: tachycardia
Metabolic and Nutritional: weight loss
Special Senses: blurred vision
Urogenital: decreased libido, anorgasmia, ejaculatory difficulty

DRUG ABUSE AND ADDICTION

Fentanyl transdermal system contains a high concentration of fentanyl, a potent Schedule II opioid agonist. Schedule II opioid substances, which include hydromorphone, methadone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Fentanyl, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

The high content of fentanyl in the patches (fentanyl transdermal system) may be a particular target for abuse and diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since fentanyl transdermal system may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Fentanyl transdermal systems are intended for transdermal use (to be applied on the skin) only. Do not use a fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way.

OVERDOSAGE

Clinical Presentation

The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious significant effect being hypoventilation.

Treatment

For the management of hypoventilation, immediate countermeasures include removing the fentanyl transdermal system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone. The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

Always ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

DOSAGE AND ADMINISTRATION

Special Precautions

Fentanyl transdermal system contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in fentanyl transdermal system may be a particular target for abuse and diversion.

Fentanyl transdermal systems are intended for transdermal use (on intact skin) only. The fentanyl transdermal system should not be used if the seal is broken, or the patch is cut, damaged, or changed in any way.

Each fentanyl transdermal system may be worn continuously for 72 hours. The next patch should be applied to a different skin site after removal of the previous transdermal system.

If problems with adhesion of the fentanyl transdermal system occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlayed with a transparent adhesive film dressing (e.g., Bioclusive™).

If the patch falls off before 72 hours, dispose of it by folding in half and flushing down the toilet. A new patch may be applied to a different skin site.

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

The concomitant use of fentanyl transdermal system with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fasamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see BOX WARNING; WARNINGS; CLINICAL PHARMACOLOGY, Drug Interactions; WARNINGS; and PRECAUTIONS for further information).

Pediatric patients converting to fentanyl transdermal system with a 25 mcg/hr patch should be opioid-tolerant and receiving at least 60 mg of oral morphine or the equivalent per day. The dose conversion schedule described in **Table C**, and method of titration described below are recommended in opioid-tolerant pediatric patients over 2 years of age with chronic pain (see **PRECAUTIONS**, **Pediatric Use**).

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Fentanyl transdermal system should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance (see **CLINICAL PHARMACOLOGY**, **Special Populations**, **Geriatric Use**).

General Principles

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that:

- **requires continuous, around-the-clock opioid administration for an extended period of time**
- **cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.**

Fentanyl transdermal system should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphone daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time.**
- **in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain (e.g., use on an as needed basis [prn])**

(See CONTRAINDICATIONS for further information.)

Safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS, Pediatric Use).

Prescribers should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

As with all opioids, dosage should be individualized. The most important factor to be considered in determining the appropriate dose is the extent of preexisting opioid-tolerance (see **BOX WARNING** and **CONTRAINDICATIONS**). Initial doses should be reduced in elderly or debilitated patients (see **PRECAUTIONS**).

Fentanyl transdermal system should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate patch removal. Hair at the application site should be clipped (not shaved) prior to system application. If the site of fentanyl transdermal system application must be cleansed prior to application of the patch, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to patch application.

Fentanyl transdermal system should be applied immediately upon removal from the sealed blister package. Do not use if the seal is broken. Do not alter the patch (e.g., cut) in any way prior to application and do not use cut or damaged patches.

The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges. If the drug matrix accidentally contacts the skin of the patient or caregiver, the skin should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents because they may enhance the drug's ability to penetrate the skin.

Fentanyl transdermal system should be kept out of the reach of children. Used patches should be folded so that the adhesive side of the patch adheres to itself, then the patch should be flushed down the toilet immediately upon removal. Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed. Unused patches should be removed from their blisters, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.

Dose Selection

Doses must be individualized based upon the status of each patient and should be assessed at regular intervals after fentanyl transdermal system application. Reduced doses of fentanyl transdermal system are suggested for the elderly and other groups discussed in PRECAUTIONS.

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression.

In selecting an initial fentanyl transdermal system dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the fentanyl transdermal system dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial Fentanyl Transdermal System Dose Selection

Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

There has been no systemic evaluation of fentanyl transdermal system as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to fentanyl transdermal system from other narcotics. The efficacy of fentanyl transdermal system 12 mcg/hr as an initiating dose has not been determined. In addition, patients who are not opioid-tolerant have experienced hypoventilation and death during use of fentanyl transdermal system. Therefore, fentanyl transdermal system should be used only in patients who are opioid-tolerant.

To convert adult and pediatric patients from oral or parenteral opioids to fentanyl transdermal system use **TABLE C**:

Alternatively, for adult and pediatric patients taking opioids or doses not listed in **TABLE C**, use the following methodology:

1. Calculate the previous 24 hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using **TABLE D**.
3. **TABLE E** displays the range of 24 hour oral morphine doses that are recommended for conversion to each fentanyl transdermal system dose. Use this table to find the calculated 24 hour morphine dose and the corresponding fentanyl transdermal system dose. Initiate fentanyl transdermal system treatment using the recommended dose and titrate patients upwards (no more frequently than every 3 days after the initial dose or than every 6 days thereafter) until analgesic efficacy is attained. The recommended starting dose when converting from other opioids to fentanyl transdermal system is likely too low for 50% of patients. This starting dose is recommended to minimize the potential for overdosing patients with the first dose. For delivery rates in excess of 100 mcg/hr, multiple systems may be used.

TABLE C[1]
DOSE CONVERSION GUIDELINES

Current Analgesic	Daily Dosage (mg/d)			
Oral morphine	60 to 134	135 to 224	225 to 314	315 to 404
IM/IV morphine	10 to 22	23 to 37	38 to 52	53 to 67
Oral oxycodone	30 to 67	67.5 to 112	112.5 to 157	157.5 to 202
IM/IV oxycodone	15 to 33	33.1 to 56	56.1 to 78	78.1 to 101
Oral codeine	150 to 447	448 to 747	748 to 1047	1048 to 1347
Oral hydromorphone	8 to 17	17.1 to 28	28.1 to 39	39.1 to 51
IV hydromorphone	1.5 to 3.4	3.5 to 5.6	5.7 to 7.9	8 to 10
IM meperidine	75 to 165	166 to 278	279 to 390	391 to 503
Oral methadone	20 to 44	45 to 74	75 to 104	105 to 134
IM methadone	10 to 22	23 to 37	38 to 52	53 to 67
	⇓	⇓	⇓	⇓
Recommended fentanyl transdermal system dose	25 mcg/hr	50 mcg/hr	75 mcg/hr	100 mcg/hr

Alternatively, for adult and pediatric patients taking opioids or doses not listed in **TABLE C**, use the conversion methodology outlined above with **TABLE D**.

[1] **TABLE C should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of TABLE C for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, Discontinuation of Fentanyl Transdermal System).**

TABLE D[a]
EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg)	
	IM[b,c]	PO
Morphine	10	60 (30)[d]
Hydromorphone (Dilaudid®)	1.5	7.5
Methadone (Dolophine®)	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)	2	4
Oxymorphone (Numorphan®)	1	10 (PR)
Meperidine (Demerol®)	75	-
Codeine	130	200

[1] **TABLE D should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of TABLE D for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, Discontinuation of Fentanyl Transdermal System).**

[a] All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

[b] Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.

[c] Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV, or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.

[d] The conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain. The conversion ratio of 10 mg parenteral morphine = 60 mg oral morphine is based on a potency study in acute pain. Reference: Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76:402-416.

TABLE E[1]
RECOMMENDED INITIAL FENTANYL TRANSDERMAL SYSTEM DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24 hour Morphine (mg/day)	Fentanyl Transdermal System Dose (mcg/hr)
60 to 134	25
135 to 224	50
225 to 314	75
315 to 404	100
405 to 494	125
495 to 584	150
585 to 674	175
675 to 764	200
765 to 854	225
855 to 944	250
945 to 1034	275
1035 to 1124	300

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal system.

[1] **TABLE E should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of TABLE E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, Discontinuation of Fentanyl Transdermal System).**

The majority of patients are adequately maintained with fentanyl transdermal system administered every 72 hours. Some patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. An increase in the fentanyl transdermal system dose should be evaluated before changing dosing intervals in order to maintain patients on a 72 hour regimen. Dosing intervals less than every 72 hours were not studied in children and adolescents and are not recommended.

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of fentanyl transdermal system cannot be made before 24 hours of wearing. The initial fentanyl transdermal system dose may be increased after 3 days (see **DOSAGE AND ADMINISTRATION, Dose Titration**).

During the initial application of fentanyl transdermal system, patients should use short-acting analgesics as needed until analgesic efficacy with fentanyl transdermal system is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for "breakthrough" pain.

Dose Titration

The recommended initial fentanyl transdermal system dose based upon the daily oral morphine dose is conservative, and 50% of patients are likely to require a dose increase after initial application of fentanyl transdermal system. The initial fentanyl transdermal system dosage may be increased after 3 days based on the daily dose of supplemental opioid analgesics required by the patient in the second or third day of the initial application.

Physicians are advised that it may take up to 6 days after increasing the dose of fentanyl transdermal system for the patient to reach equilibrium on the new dose (see graph in **CLINICAL PHARMACOLOGY**). Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/hr increase in fentanyl transdermal system dose.

Discontinuation of Fentanyl Transdermal System

To convert patients to another opioid, remove fentanyl transdermal system and titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion or dose adjustment. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

TABLES C, D, and E should not be used to convert from fentanyl transdermal system to other therapies. Because the conversion of fentanyl transdermal system is conservative, use of TABLES C, D, and E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.

HOW SUPPLIED

Fentanyl transdermal system is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems:

Label Strength (mcg/hr)	Patch Size (cm^2)	Fentanyl Content (mg)
25	10.7	2.76
50	21.4	5.52
75	32.1	8.28
100	42.8	11.04

Safety and Handling

Fentanyl transdermal systems are supplied in sealed blister packages which pose little risk of exposure to health care workers. If the drug matrix accidentally contacts the skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents because they may enhance the drug's ability to penetrate the skin. Do not use a fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way.

KEEP FENTANYL TRANSDERMAL SYSTEM OUT OF THE REACH OF CHILDREN AND PETS.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Apply immediately after removal from individually sealed blister package. Do not use if the seal is broken. **For transdermal use only.**

A SCHEDULE CII NARCOTIC. DEA ORDER FORM REQUIRED.

Manufactured By:
Aveva Drug Delivery Systems
A Nitto Denko Company
Miramar, FL 33025
Distributed By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2008

Medication Guide
Fentanyl Transdermal System C II
℞ only

IMPORTANT:

- **Keep fentanyl transdermal system in a safe place away from children and pets. Accidental use by a child or pet is a medical emergency and may result in death. If a child or pet accidentally uses fentanyl transdermal system, get emergency help right away.**
- **Make sure you read the separate "Instructions for Applying a Fentanyl Transdermal System." Always use a fentanyl transdermal system the right way. Fentanyl transdermal system can cause serious breathing problems and death, especially if it is used the wrong way.**
- **Fentanyl transdermal system is a federally controlled substance (C-II) because it can be abused. Keep fentanyl transdermal system in a safe place to prevent theft. Selling or giving away fentanyl transdermal system may harm others, and is against the law.**
- **Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.**

Read the Medication Guide that comes with fentanyl transdermal system before you start using it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Make sure you read and understand all the instructions for using fentanyl transdermal system. Do not use fentanyl transdermal system unless you understand everything. Talk to your healthcare provider if you have questions.

What is the most important information I should know about fentanyl transdermal system?

Fentanyl transdermal system is a skin patch that contains fentanyl. **Fentanyl is a very strong opioid narcotic pain medicine that can cause serious and life-threatening breathing problems. Serious and life-threatening breathing problems can happen because of an overdose or if the dose you are using is too high for you. Call your doctor right away or get emergency medical help if you:**

- have trouble breathing, or have slow or shallow breathing
- have a slow heartbeat
- have severe sleepiness
- have cold, clammy skin
- feel faint, dizzy, confused, or cannot think, walk, or talk normally
- have a seizure
- have hallucinations

Fentanyl transdermal system is only for adults and children over the age of two with persistent, moderate to severe chronic pain and who:

- are already using another strong opioid narcotic pain medicine around-the-clock, and have been using the medicine regularly for a week or longer. This is called being opioid-tolerant
- have pain that cannot be controlled with other medicines

Do not use fentanyl transdermal system:

- **if you are not already using another opioid narcotic medicine and are not opioid tolerant**
- if you need opioid pain medicines for only a short time
- for pain from surgery, medical or dental procedures
- if your pain can be taken care of by occasional use of other pain medicines
- in children who are less than 2 years of age
- if you have asthma symptoms or have severe asthma

A fentanyl transdermal system must be used only on the skin of the person for whom it was prescribed. If the patch comes off and accidentally sticks to the skin of another person, take the patch off of that person right away, wash the area with water, and get medical care for them right away.

Fentanyl transdermal system is not safe for everyone. Tell your doctor about all of your medical conditions.

Tell your doctor if you are planning to become pregnant, are pregnant, or breastfeeding. Fentanyl transdermal system may cause serious harm to a baby.

Tell your doctor about all the medicines you take. Some medicines may cause serious or life-threatening side effects when used with fentanyl transdermal system. Your doctor will tell you if it is safe to take other medicines while you are using fentanyl transdermal system.

Know the medicines you take. Keep a list of your medicines to show to your doctor and pharmacist.

How should I use fentanyl transdermal system?

Read the separate "Instructions for Applying a Fentanyl Transdermal System."

- **You must always use** fentanyl transdermal systems the right way:
  - **Do not** use a fentanyl transdermal system if the seal is broken, or the patch is cut, damaged, or changed in any way.
  - **Do not** use heat sources such as heating pads, electric blankets, heat lamps, tanning lamps, saunas, hot tubs, or heated waterbeds while wearing a fentanyl transdermal system.
  - **Do not** take hot baths or sunbathe while wearing a fentanyl transdermal system.
- **If you have problems with the fentanyl transdermal system not sticking:**
  1. Apply first aid tape only to the edges of the patch.
  2. If problems with the patch not sticking persist, cover the patch with Bioclusive™. This is a special see-through adhesive dressing. **Never cover a fentanyl transdermal system with any other bandage or tape.**
- **If your fentanyl transdermal system falls off before 3 days or 72 hours, fold the sticky side together and flush down a toilet. Put a new one on at a different skin site.**
- **Do not change your dose unless your doctor tells you to.** Your doctor may change your dose after seeing how the medicine affects you. Do not use fentanyl transdermal system more often than prescribed. Call your doctor if your pain is not well controlled while using fentanyl transdermal system.
- **Do not stop using fentanyl transdermal system suddenly.** Stopping fentanyl transdermal system suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). Your body can develop a physical dependence on fentanyl transdermal system. If your doctor decides you no longer need fentanyl transdermal system, ask how to slowly reduce this medicine so you don't have withdrawal symptoms. Do not stop taking fentanyl transdermal system without talking to your doctor.
- **Do not wear more than one fentanyl transdermal system at a time**, unless your doctor tells you to do so.
- **Call your doctor right away if**
  - **You get a fever higher than 102°F**
  - Your body temperature increases from exercise.

A fever or increase in body temperature may cause too much of the medicine in fentanyl transdermal system to pass into your body.

- **If you use more fentanyl transdermal systems than your doctor has prescribed, get emergency medical help right away.**
- **Do not drink any alcohol while using fentanyl transdermal system.** Alcohol can increase your chances of having serious side effects.
- **Do not drive, operate heavy machinery, or do other possibly dangerous activities** until you know how fentanyl transdermal system affects you. Fentanyl transdermal system can make you sleepy. Ask your doctor to tell you when it is okay to do these activities.
- When you remove your fentanyl transdermal system, fold the sticky sides of a used fentanyl transdermal system together and flush it down the toilet. **Do not put used fentanyl transdermal systems in a trash can.**

What are the possible side effects of fentanyl transdermal system?

Serious side effects include:

- **Life-threatening breathing problems.** See **"What is the most important information I should know about fentanyl transdermal system?"**
- **Low blood pressure.** This can make you feel dizzy if you get up too fast from sitting or lying down.

The common side effects with fentanyl transdermal system are nausea, vomiting, constipation, dry mouth, sleepiness, confusion, weakness, sweating, and pain and redness where the patch was applied.

Constipation is a very common side effect of all opioid medicines. Talk to your doctor about the use of laxatives and stool softeners to prevent or treat constipation while taking fentanyl transdermal system.

Talk to your healthcare provider about any side effect that concerns you.

These are not all the possible side effects of fentanyl transdermal system. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store fentanyl transdermal system?

- Store fentanyl transdermal system at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
- Keep a fentanyl transdermal system in its protective blister until you are ready to use it.
- **Keep fentanyl transdermal system in a safe place out of the reach of children and pets.**
- Dispose of fentanyl transdermal systems you no longer need. Open the unused blisters, fold the sticky sides of the patches together, and flush them down the toilet.

General information about the safe and effective use of fentanyl transdermal system

- Do not use fentanyl transdermal system for a condition for which it was not prescribed.
- **Do not give fentanyl transdermal system to other people, even if they have the same symptoms you have. Fentanyl transdermal system can harm other people and even cause death. Sharing fentanyl transdermal system is against the law.**
- This Medication Guide summarizes the most important information about fentanyl transdermal system. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about fentanyl transdermal system that is written for doctors.

For questions about fentanyl transdermal system, call Teva Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS. If this is a medical emergency, please call 911.

What are the ingredients of fentanyl transdermal system?

Active ingredient: fentanyl

Inactive ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

This Medication Guide has been approved by the United States Food and Drug Administration.

Manufactured By:
Aveva Drug Delivery Systems
A Nitto Denko Company
Miramar, FL 33025
Distributed By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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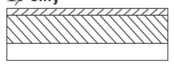
Fentanyl Transdermal System C II
Instructions for Applying a Fentanyl Transdermal System
℞ only



IMPERMEABLE BACKING
FENTANYL IN POLYISOBUTENE ADHESIVE MATRIX
RELEASE LINER

Before Applying Fentanyl Transdermal System

- **Fentanyl transdermal system is a patch with medicine inside. The patch is designed to keep the medicine from getting on your hands or body. If the medicine accidentally gets on your skin, wash the area with large amounts of water only. Do not use soap, alcohol, lotions, oils, or other products to remove the medicine because they may increase the medicine's ability to go through the skin.**
- **Each fentanyl transdermal system is sealed in its own protective blister. Do not remove a fentanyl transdermal system from the blister until you are ready to use it.**
- **Do not use a fentanyl transdermal system if the seal is broken or the patch is cut, damaged or changed in any way.**
- **Fentanyl transdermal systems are available in 4 different doses and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.**

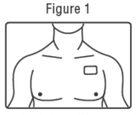
Applying a Fentanyl Transdermal System

1. Skin Areas Where the Fentanyl Transdermal System May Be Applied:

For adults:

- Put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair (see **Figures 1** to **4**).

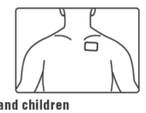
Figure 1



For children (and adults with mental impairment):

- **Put the patch on the upper back (see Figure 2).** This will lower the chances that the child will remove the patch and put it in their mouth.

Figure 2



For adults and children

- Do not put a fentanyl transdermal system on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.

Figure 3

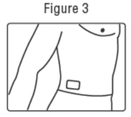
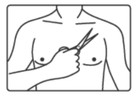


Figure 4

- Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin).** Instead, clip hair as close to the skin as possible (see **Figure 5**).

Figure 5



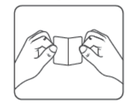
- **Talk to your doctor if you have questions about skin application sites.**

2. Prepare to Apply a Fentanyl Transdermal System:

- Choose the time of day that is best for you to apply fentanyl transdermal system. Change it at about the same time of day (3 days or 72 hours after you apply the patch) or as directed by your doctor.
- Do not wear more than one fentanyl transdermal system at a time unless your doctor tells you to do so. Before putting on a new fentanyl transdermal system, remove the patch you have been wearing.
- Clean the skin area with clear water **only. Pat skin completely dry.** Do not use anything on the skin such as soaps, lotions, oils, or alcohol before the patch is applied.

3. Each fentanyl transdermal system is sealed in its own protective blister. Do not remove the fentanyl transdermal system from the blister until you are ready to use it. When you are ready to put on the fentanyl transdermal system, hold the blister so that the fentanyl transdermal system is visible and cut through blister package taking care not to cut through the fentanyl transdermal system. Remove the fentanyl transdermal system from the blister (See **Figure 6**).

Figure 6



4. Peel: Peel the liner from the back of the patch one half at a time (see **Figures 7** and **8**) and throw away. **Touch the sticky side as little as possible.**

Figure 7

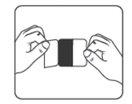
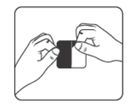
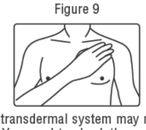


Figure 8



5. Press: Press the patch onto the chosen skin site **with the palm of your hand and hold there for at least 30 seconds** (see **Figure 9**). Make sure it sticks well, especially at the edges.

Figure 9



- Fentanyl transdermal system may not stick to all patients. You need to check the patches often to make sure that they are sticking well to the skin.
- If the patch falls off right away after applying, throw it away and put a new one on at a different skin site (see **Disposing a Fentanyl Transdermal System**).
- If you have a problem with the patch not sticking
  - Apply first aid tape only to the edges of the patch.
  - If you continue to have problems with the patch sticking, you may cover the patch with Bioclusive™. This is a special see-through adhesive dressing. **Never cover a fentanyl transdermal system with any other bandage or tape.** Remove the backing from the Bioclusive™ dressing and place it carefully over the fentanyl transdermal system, smoothing it over the patch and your skin.
- **If your patch falls off later, but before 3 days (72 hours) of use, discard it properly (see Disposing a Fentanyl Transdermal System) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).**

6. Wash your hands when you have finished applying a fentanyl transdermal system.

7. Remove a fentanyl transdermal system after wearing it for 3 days (72 hours) (see **Disposing a Fentanyl Transdermal System**). Choose a **different** place on the skin to apply a new fentanyl transdermal system and repeat Steps 2 through 6.

Do not apply the new patch to the same place as the last one.

Water and Fentanyl Transdermal System

- You can bathe, swim or shower while you are wearing a fentanyl transdermal system. If the patch falls off before 3 days (72 hours) after application, discard it properly (see **Disposing a Fentanyl Transdermal System**) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).

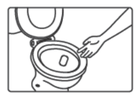
Disposing a Fentanyl Transdermal System

- Fold the used fentanyl transdermal system in half so that the sticky side sticks to itself **(Figure 10). Flush the used fentanyl transdermal system down the toilet right away (Figure 11). A used fentanyl transdermal system CAN be VERY dangerous for or even lead to death in babies, children, pets, and adults who have not been prescribed fentanyl transdermal system.**

Figure 10

- Throw away any fentanyl transdermal systems that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective blister and remove the protective liner. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet.** Do not flush the blister or the protective liner down the toilet. These items can be thrown away in a trashcan.

Figure 11



Manufactured By:
Aveva Drug Delivery Systems
A Nitto Denko Company
Miramar, FL 33025
Distributed By:
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Sellersville, PA 18960

Iss. 7/2008

NDC 0093-**6900**-19 **One** (25 mcg/hr) **System**

Fentanyl Transdermal System, 25 mcg/hr C II

In vivo **delivery of 25 mcg/hr fentanyl for 72 hours**

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 2.76 mg fentanyl and the following Inactive ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner.

Do not expose area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF REACH OF CHILDREN

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

Iss. 7/2008
4001090
Rev. 08/08

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Manufactured By:
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Miramar, FL 33025

℞ **only**

(01)003 0093 6900 19 2

ONLY for pain requiring opioid medicine around-the-clock

NDC 0093-**6901**-19 **One** (50 mcg/hr) **System**

Fentanyl Transdermal System, 50 mcg/hr C II

In vivo **delivery of 50 mcg/hr fentanyl for 72 hours**

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 5.52 mg fentanyl and the following Inactive ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner.

Do not expose area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF REACH OF CHILDREN

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

Iss. 7/2008
4001091
Rev. 08/08

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℞ **only**

(01)003 0093 6901 19 9

ONLY for pain requiring opioid medicine around-the-clock

NDC 0093-**6902**-19 **One** (75 mcg/hr) **System**

Fentanyl Transdermal System

CII

75 mcg/hr

In vivo **delivery of 75 mcg/hr fentanyl for 72 hours**

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 8.28 mg fentanyl and the following inactive ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner.

Do not expose area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF REACH OF CHILDREN

4001100 Iss. 7/2008
Rev. 08/08 ℞ **only**

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

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(01)003 0093 6902 19 6

ONLY for pain requiring opioid medicine around-the-clock

NDC 0093-**6903**-19 **One** (100 mcg/hr) **System**

Fentanyl Transdermal System, 100 mcg/hr

C II

***In vivo* delivery of 100 mcg/hr fentanyl for 72 hours**

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 11.04 mg fentanyl and the following inactive ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner.

Do not expose area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF REACH OF CHILDREN

4001101 Iss. 7/2008
Rev. 08/08 ℞ **only**

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

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Manufactured By:
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Miramar, FL 33025

(01)003 0093 6903 19 3

ONLY for pain requiring opioid medicine around-the-clock

Each transdermal system contains: 2.76 mg fentanyl.

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF THE REACH OF CHILDREN

Inactive Ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner. Do not expose the area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

See Medication Guide for important safety information.

For your convenience in recording narcotic use,

INITIAL/DATE

1._____ 2._____ 3._____ 4._____ 5._____

For questions about fentanyl transdermal system, call TEVA Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS. If this is a medical emergency, please call 911.

Manufactured By: Iss. 7/2008

AVEVA DRUG DELIVERY SYSTEMS
A Nitto Denko Company

Miramar, FL 33025

Distributed By:
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Sellersville, PA 18960

ONLY for pain requiring opioid medicine around-the-clock

1 0093-6900-45 3
N

ONLY for pain requiring opioid medicine around-the-clock

Because it can cause troublе breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:
- For short term or any post-operative pain, or occasional pain as-needed opioid medication
- For mild pain or pain that can be treated with non-opioid or
- Unless you have been using other narcotic opioid medicines (must be opioid tolerant)

In vivo delivery of 25 mcg/hr fentanyl for 72 hours

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

℞ only

NDC 0093-6900-45

FENTANYL TRANSDERMAL SYSTEM

25 mcg/hr

TEVA

5 SYSTEMS

Five (25 mcg/hr) Systems

3001667 Rev. 08/08

FENTANYL TRANSDERMAL SYSTEM
25 mcg/hr

Each transdermal system contains: 5.52 mg fentanyl.

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF THE REACH OF CHILDREN

Inactive Ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner. Do not expose the area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

See Medication Guide for important safety information.

For your convenience in recording narcotic use,

INITIAL/DATE

1.________ 2.________ 3.________ 4.________ 5.________

For questions about fentanyl transdermal system, call TEVA Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS. If this is a medical emergency, please call 911.

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Sellersville, PA 18960

ONLY for pain requiring opioid medicine around-the-clock

3 N 0093-6901-45 8

NDC 0093-6901-45

FENTANYL TRANSDERMAL SYSTEM CII

50 mcg/hr

In vivo delivery of 50 mcg/hr fentanyl for 72 hours

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- For short term or any post-operative pain, or occasional pain
- For mild pain or pain that can be treated with non-opioid or as-needed opioid medication
- Unless you have been using other narcotic opioid medicines (must be opioid tolerant)

ONLY for pain requiring opioid medicine around-the-clock

℞ only

TEVA

5 SYSTEMS

Five (50 mcg/hr) Systems

FENTANYL CII
TRANSDERMAL SYSTEM
50 mcg/hr

3001668 Rev. 08/08

Each transdermal system contains: 8.28 mg fentanyl.

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF THE REACH OF CHILDREN

Inactive Ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner. Do not expose the area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

See Medication Guide for important safety information.

For your convenience in recording narcotic use,

INITIAL/DATE

1._____ 2._____ 3._____ 4._____ 5._____

For questions about fentanyl transdermal system, call TEVA Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS. If this is a medical emergency, please call 911.

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Miramar, FL 33025

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Sellersville, PA 18960

ONLY for pain requiring opioid medicine around-the-clock

2 0093-6903-45 3 N

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:
- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

ONLY for pain requiring opioid medicine around-the-clock

℞ only

In vivo **delivery of 75 mcg/hr fentanyl for 72 hours**

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

NDC 0093-6902-45

FENTANYL TRANSDERMAL SYSTEM

75 mcg/hr

Five (75 mcg/hr) Systems

5 SYSTEMS

TEVA

3001669 Rev. 08/08

FENTANYL TRANSDERMAL SYSTEM
75 mcg/hr

3001670 Rev. 08/08

NDC 0093-**6903**-45

Five (100 mcg/hr) **Systems**

FENTANYL CII
TRANSDERMAL SYSTEM
100 mcg/hr

5 SYSTEMS

TEVA

In vivo delivery of 100 mcg/hr fentanyl for 72 hours

℞ only

Read enclosed Fentanyl Transdermal System Medication Guide for important safety information.

Because it can cause trouble breathing which can be fatal,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:
- For short term or any post-operative pain, or occasional pain
- For mild pain or pain that can be treated with non-opioid or as-needed opioid medication
- Unless you have been using other narcotic opioid medicines (must be opioid tolerant)

ONLY for pain requiring opioid medicine around-the-clock

FENTANYL CII
TRANSDERMAL SYSTEM
100 mcg/hr

N 3 0093-6903-45 2

Each transdermal system contains: 11.04 mg fentanyl

DO NOT USE IF SEAL ON BLISTER IS BROKEN

KEEP OUT OF THE REACH OF CHILDREN

Inactive Ingredients: isopropyl myristate, octyldodecanol, polybutene, and polyisobutene adhesive.

Usual Dosage: For information for use see accompanying product literature.

Apply immediately upon removal from blister and after removal of the protective liner. Do not expose the area to heat. Do not store unblistered and store blisters at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

See Medication Guide for important safety information.

For your convenience in recording narcotic use,

INITIAL/DATE

1.______ 2.______ 3.______ 4.______ 5.______

For questions about fentanyl transdermal system, call TEVA Pharmaceuticals at 1-888-838-2872, MEDICAL AFFAIRS. If this is a medical emergency, please call 911.

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Sellersville, PA 18960

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-449 Date of Submission: March 21, 2005 and June 15, 2005

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

Labeling Deficiencies:

1. BLISTER - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   a. We note that you proposed use of a blister rather than a pouch, and the blister packaging system consists of a (b) (4) pouchstock and a (b) (4) tray. Please further describe your packaging configuration to aid our understanding of the system and submit the labels for our review.

   b. Please assure that your proposed labels contain similar information appearing on the innovator's pouch configuration and/or comment.

2. UNIT BACKING

   Please verify that the backing contains the established name and strength in a clearly legible manner as does the innovator's. Submit a sample of the backing for our review. In addition, please verify that the ink used for printing on the unit backing does not leach through to the transdermal system.

3. CARTON - 5 systems

   a. It is preferable to use the term "hr" for hour rather than "h".

   b. Include the text " (b) (4) in a prominent manner for all strengths. We refer you to the innovator's carton labeling for guidance.

   c. You may delete " (b) (4) " from the listing of inactive ingredients since this is not a part of the formulation of your dug product.

   d. We encourage the enclosing of the statement " (b) (4) to enhance the prominence as does the innovator.

4. INSERT

   a. GENERAL

      i. See comment 3(a) above.

      ii. We acknowledge that you are not seeking the approval of pediatric information protected by the exclusivity until expiration of the innovator's exclusivity right. However, we regard all pediatric information subject to the exclusivity as safety information. We request that all pediatric information be retained in your labeling. We refer you to 21 CFR

314.127(a)(7) for guidance.

iii. Please note that the innovator's labeling was last approved February 4, 2005. Please revise your labeling accordingly.

iv. We note that your proposed drug product has a matrix system as opposed to the innovator's reservoir system. Please remove any statements specific to the reference-listed drug and/or replace with the text specific to your drug product.

v. Replace "Duragesic" or "Duragesic patch" with "fentanyl transdermal system" throughout the text. [rather than " (b) (4) (b) (4)]

b. PATIENT INFORMATION LEAFLET

i. See comments under GENERAL above, wherever applicable.

ii. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply and how will these leaflets be supplied.

Please revise as directed above, and submit the revised labels and labeling in draft as an amendment to this unapproved application. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTE TO CHEMIST

1. **The sponsor's drug product system is different from that of the RLD.**

2. **Please note that the sponsor's drug product contains 2.76 mg, 5.52 mg, 8.28 mg, and 11.04 mg fentanyl whereas the Duragesic® patch contains 2.5 mg, 5 mg, 7.5 mg, & 10 mg fentanyl, respectively.**

3. **The sponsor's drug products do not contain "alcohol", not like the innovator's product**

FOR THE RECORD:

1. MODEL LABELING - The generic labeling template developed using Duragesic® package insert labeling and patient information leaflet (NDA 19-813/S-036, approved 5/20/03). In the process of developing the generic labeling template, a decision was made to include all new pediatric information of the RLD protected by the exclusivity in consultation with HFD-170, Pediatric Labeling Team and OCC as all this information was regarded as safety information. However, the Duragesic® labeling has been updated approved in S-039 (approved 2/4/05) so the generic labeling has also been updated accordingly.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2895 (Volume B.1.2).

4. PATENTS/EXCLUSIVITIES

All patents are expired.

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
019813	001	NPP	MAY 20,2006	(Revised per BPCA)
019813	001	PED	NOV 20,2006	(Revised per BPCA)

U- 43: MANAGEMENT OF CHRONIC PAIN IN PATIENTS REQUIRING OPIOID ANALGESIA

The sponsor proposed to carve out the protected pediatric information to seek an approval prior to the expiration of the exclusivity. However, we will have the sponsor include all information. See FTR#1.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISONS

RLD - Do not store above 77°F (25°C).

ANDA - Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature]

6. PACKAGING CONFIGURATIONS

RLD & ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

7. CONTAINER/CLOSURE

P. 4450, B.1.2

(b) (4) pouchstock and material and (b) (4) tray. The (b) (4) pouchstock is the same material approved in Aveva Drug Delivery System's Nicotine Transdermal systems (NDA 19-983). It is CRC.

8. This drug product is being manufactured by Aveva Drug Delivery System, Inc.

Date of Review: 9/13/05 **Date of Submission: 3/21/05 & 6/15/05**

Primary Reviewer: Chan Park **Date:** 9/20/05

Team Leader: Lillie Golson **Date:** 9/20/05

cc:

ANDA: 77-449
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-449 Date of Submission: June 5, 2006

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

Labeling Deficiencies:

1. BLISTER - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   a. We note that your proposed blister is designed in a manner that only one side of the blister bears all information as opposed to the innovator's pouch, which distributes the information on both sides. We are concerned because the information appears too cluttered. If your package design does not permit information being printed on both front and back panels, we recommend that you relocate the same information appearing on the Duragesic® pouch's back panel to your carton labeling, except the name and place of business. You may delete either the "Manufactured by" or "Distributed by" statement to secure more space. If you choose to use the "Manufactured by" statement, include the address as it appears on your carton labeling.

   b. Increase the prominence of the established name and strength by increasing size and other means. These should appear most prominent on the label.

   c. Please differentiate the strengths of your drug products by using boxing, contrasting colors, and/or some other means. We refer you to the innovator's pouch for guidance.

   d. Include the text "(b) (4)" in a prominent manner. We refer you to the innovator's pouch for guidance.

   e. Relocate the controlled substance symbol further away from the strength.

   f. List inactive ingredients as does the innovator.

   g. Please ensure that blister labels contain the National Drug Code (NDC) number in a linear bar code format. We refer you to the final rule posted in the Federal Register: February 26, 2004 (Volume 69, Number 38) for guidance.

2. CARTON - 5 systems

   a. See comments under BLISTER, whichever applicable.

   b. Include the text "(b) (4)" on both panels 1 and 3 in a prominent manner similar to the innovator's carton.

3. UNIT BACKING

   a. We acknowledge your comment that the ink used for printing will not leach through to the system.

   b. Please submit the unit backing sample with established name and strength printed in a clearly legible manner.

4. INSERT

a. GENERAL

i. Delete the term "the" associated with the drug name "fentanyl transdermal system" throughout the text as it is not part of the established name.

ii. Add a hyphen after the prefix "post" of "pre" throughout the text. [e.g., post-marketing, pre-existing, etc.]

b. DESCRIPTION (System Components and Structure) - Include the following text immediately prior to the schematic diagram of the transdermal system:

Before use, a protective liner covering the adhesive layer is removed and discarded.

c. CLINICAL PHARMACOLOGY - Pharmacokinetics:

i. Figure - Revise the title to read:

... Multiple Applications of A Fentanyl Transderamal... [add "A"]

ii. Table A - Revise the title to read:

...HOUR APPLICATION OF A FENTANYL TRANSDERMAL... [add "A"]

d. PRECAUTIONS - Pregnancy: Pregnancy Category C:

Revise this subsection heading to read "Pregnancy: Teratogenic Effects: Pregnancy Category C". We refer you to 21 CFR 201.57(f)(6).

e. DOSAGE AND ADMINISTRATION

i. Special Precautions:

Underline the second paragraph as does the innovator.

ii. Dose Titration - Revise the third paragraph to read:

...the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/hr increase in...

f. PATIENT INFORMATION LEAFLET

a. What is fentanyl transdermal system? - 1st paragraph:

...because it is a strong opioid narcotic pain... [add "opioid"]

b. How and where to apply fentanyl transdermal system -1st bullet after the instruction #3:

Please include an instruction as to how to open the blister rather than inclusion of the plain statement "(b) (4)", reflecting the information on the blister package. We refer you to the innovator's patient information leaflet.

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at

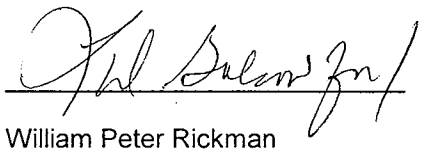
http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf. and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD for your proposed drug product is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained



William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTE TO CHEMIST

1. **The sponsor's drug product system is different from that of the RLD.**

2. **Please note that the sponsor's drug product contains 2.76 mg, 5.52 mg, 8.28 mg, and 11.04 mg fentanyl whereas the Duragesic® patch contains 2.5 mg, 5 mg, 7.5 mg, & 10 mg fentanyl, respectively.**

3. **The sponsor's drug products do not contain "alcohol", whereas the innovator 's does. In addition, the sponsor's system is a Matrix system as opposed to the Reservoir system of the innovator's.**

4. **The sponsor stated that the ink used on the backing of the patch does not leach through to the system. They submitted supporting data to verify their statement. Is their statement accurate?**

FOR THE RECORD:

1. MODEL LABELING - The generic labeling template developed using Duragesic® package insert labeling and patient information leaflet (NDA 19-813/S-036, approved 5/20/03). In the process of developing the generic labeling template, a decision was made to include all new pediatric information of the RLD protected by the exclusivity in consultation with HFD-170, Pediatric Labeling Team and OCC as all this information was regarded as safety information. However, the Duragesic® labeling has been updated approved in S-039 (approved 2/4/05) so the generic labeling has also been updated accordingly.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2895 (Volume B.1.2).

4. PATENTS/EXCLUSIVITIES

All patents are expired.

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
019813	001	NPP	MAY 20,2006	(Revised per BPCA)
019813	001	PED	NOV 20,2006	(Revised per BPCA)

The sponsor proposed to carve out the protected pediatric information to seek an approval prior to the expiration of the exclusivity. However, we will have the sponsor include all information. See FTR#1.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISONS

RLD - Do not store above 77°F (25°C).

ANDA - Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature]

6. PACKAGING CONFIGURATIONS

RLD & ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

7. CONTAINER/CLOSURE

P. 4450, B.1.2

(b) (4) pouchstock and material and (b) (4) tray. The (b) (4) pouchstock is the same material approved in Aveva Drug Delivery System's Nicotine Transdermal systems (NDA 19-983). It is CRC.

8. This drug product is being manufactured by Aveva Drug Delivery System, Inc.

9. The ink used for the backing unit is the same one used for the approved NDA 19-983 (Nicotine Transdermal System). (vol. 5.1)

10. The sponsor proposed one PPI per the carton of 5 systems as does the innovator.

11. Regarding the comment on adding "a" in association with the fentanyl TDS in the pharmacokinetics subsection, see e-mail below:

From: Golson, Lillie D
Sent: Sunday, March 26, 2006 3:35 PM
To: Park, Chan H
Cc: Conner, Dale P; Golson, Lillie D; Rickman, William P; Sanchez, Aida L
Subject: FW: Control Doc.- fentanyl patches

Hi Chan,

I spoke with Dale about ways we could more accurately reflect the information in the title of the tables and charts of the pK section of the Clinical Pharmacology for the fentanyl patches to show that the data came from a product other than the ANDA holders. In discussing with John, we decided that adding the word "a" before fentanyl transdermal system in the two titles where "Duragesic" currently appears is the simplest way to address this. The labeling remains basically "the same as..." and reflects that the study was done on "a" system, not necessarily the ANDAs. I would recommend that we make the same change in the other fentanyl applications.

Thanks Dale for your input. Lillie

Date of Review: 9/5/06 **Date of Submission: 6/5/06**

Primary Reviewer: Chan Park **Date:** 9/22/06

Team Leader: Lillie Golson **Date:** 9/22/06

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cc:

ANDA: 77-449
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-449 Date of Submission: April 26, 2007, March 14, 2008 and June 18, 2008

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

Labeling Deficiencies:

1. GENERAL COMMENT

   Please be advised that the innovator's proposal for the Risk Management Plan (RMP) submitted as a labeling supplement is still under review by the Agency. You may be required to submit the similar proposal upon approval of the innovator's RMP.

2. BLISTER - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   a. As addressed in the last deficiency letter, the text on your proposed blister appears too cluttered, particularly with inclusion of new safety information approved for Durasegic® Patch. This may lead to potential medication error. In addition, the direction for removing fentanyl transdermal system from the blister is not very clear as appearing in the "Instructions for Applying Fentanyl Transdermal System". This may predispose the system to cutting or damaging when removing from the blister as the patient needs to cut through blister taking care not to cut through the fentanyl transdermal system according to your proposal.

   b. For the reasons described above, we strongly recommend that you reconfigure your packaging to be the same as the innovator's *i.e.* pouch, rather than blister and/or comment. If you change the packaging as directed, then you need to submit the CMC information associated with the new packaging. In addition, please revise all labeling pieces accordingly.

   c. "USUAL DOSAGE" rather than "DOSAGE"

3. CARTON - 5 systems

   a. See comment 2(c) above.

   b. Please relocate the text and lines associated with recording of narcotic use to the back panel to be the same as the innovator's. We believe that the text on the side panel may be subject to overlook.

4. UNIT BACKING

   The text on the blister backing for the 50 mcg/hr and 75 mcg/hr submitted April 26, 2007 is not sufficiently prominent. Please enhance the prominence that the name and strength of the drug product is readily legible.

5. INSERT

   a. GENERAL

      i. Please replace either "Duragesic®" or "Durasegic® Patch" found in the innovator's labeling with "fentanyl transdermal system". Please be advised that the established name of your drug product is "fentanyl transdermal system", not "(b) (4).

ii. We note that your drug product has matrix system as opposed to the innovator's reservoir system, yet you included the same text found in the innovator's labeling "Using a patch that is cut, damages, or changed in any way can expose the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal." in many places throughout the insert labeling. Is this an accurate statement for your drug product? This information may be specific to the reservoir system. Please delete and/or comment.

b. CLINCIAL PHARMACOLOGY - Pharmacokinetics:

We note that you included information regarding the pharmacokinetic study with or without overlay (*i.e.,* Bioclusive™ Overlay) to be in accordance with the innovator's labeling. We acknowledge that you submitted the overlay study to the Agency on June 3, 2008, which is under review. Please be advised that we defer the approval of your proposal pending your pharmacokinetic study associated with overlay.

c. PRECAUTIONS - Information for Patients, item #8:

See comment 5(b) above.

d. DOSAGE AND ADMINISTRATION

i. Special Precautions:

See comment 5(b) above.

ii. 7th paragraph, last sentence:

…Drug Interaction; WARNINGS and PRECAUTIONS… [add "WARNINGS"]

iii. Dose Selection - Table D:

Please include the proprietary names as appearing in the innovator's labeling and include the disclaimer statement for these names.

6. MEDICATION GUIDE

a. GENERAL

See comment 5(a) above.

b. TITLE

It is preferable to include the term "Rx Only".

c. How should I use…Transdermal System - 2nd bullet:

See comment 5(b) above.

d. Please include the name and place of business at the end of the medication guide.

7. INSTRUCTIONS FOR APPLYING A FENTANYL TRANSDERAMAL SYSTEM

a. See comment 5(a) above.

b. Applying a Fentanyl Transdermal system - Item #3:

See comment (2) under BLISTER above. The instruction for removal of the

system from the blister without causing any potential damage is not very clear to follow.

c. Applying a Fentanyl Transdermal System -Item #5, 3rd bullet:

See comment 5(b) above.

Revise your labeling, as instructed above, and submit electronically in final printed format. We will not ask final printed labeling pending the issue associated with the overlay study.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

NOTE TO CHEMIST

1. The sponsor's drug product system is different from that of the RLD. We asked the sponsor to revise the packaging to be the same as the innovator's, *i.e*. pouch.

2. Please note that the sponsor's drug product contains 2.76 mg, 5.52 mg, 8.28 mg, and 11.04 mg fentanyl whereas the Duragesic® patch contains 2.5 mg, 5 mg, 7.5 mg, & 10 mg fentanyl, respectively.

3. The sponsor's drug products do not contain "alcohol", whereas the innovator 's does. In addition, the sponsor's system is a Matrix system as opposed to the Reservoir system of the innovator's.

4. The sponsor stated that the ink used on the backing of the patch does not leach through to the system. They submitted supporting data to verify their statement. Is their statement accurate?

FOR THE RECORD:

1. MODEL LABELING - Duragesic® Patch (NDA 19-813/S-033), approved 2/7/08.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2895 (Volume B.1.2).

4. PATENTS/EXCLUSIVITIES

   All patents and exclusivities are expired.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISONS

   RLD - Do not store above 77^{o}F (25^{o}C).

   ANDA - Store at 20 to 25^{o}C (68 to 77^{o}F). [see USP Controlled Room Temperature]

6. PACKAGING CONFIGURATIONS

   RLD - 5s of 12.5 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

   ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

7. CONTAINER/CLOSURE

P. 4450, B.1.2
(b) (4) pouchstock and material and (b) (4) tray. The (b) (4) pouchstock is the same material approved in Aveva Drug Delivery System's Nicotine Transdermal systems (NDA 19-983). It is CRC.

8. This drug product is being manufactured by Aveva Drug Delivery System, Inc.

9. The ink used for the backing unit is the same one used for the approved NDA 19-983 (Nicotine Transdermal System). (vol. 5.1)

10. Regarding the comment on adding "a" in association with the fentanyl TDS in the pharmacokinetics subsection, see e-mail below:

From: Golson, Lillie D
Sent: Sunday, March 26, 2006 3:35 PM
To: Park, Chan H
Cc: Conner, Dale P; Golson, Lillie D; Rickman, William P; Sanchez, Aida L
Subject: FW: Control Doc.- fentanyl patches

Hi Chan,

I spoke with Dale about ways we could more accurately reflect the information in the title of the tables and charts of the pK section of the Clinical Pharmacology for the fentanyl patches to show that the data came from a product other than the ANDA holders. In discussing with John, we decided that adding the word "a" before fentanyl transdermal system in the two titles where "Duragesic" currently appears is the simplest way to address this. The labeling remains basically "the same as..." and reflects that the study was done on "a" system, not necessarily the ANDAs. I would recommend that we make the same change in the other fentanyl applications.

Thanks Dale for your input. Lillie

11. The overlay study the sponsor submitted 6/3/08 is under review by the Bio division.

12. The revised labeling submitted 6/18/08 includes information associated with the overlay study with Bioclusive™ overlay.

Date of Review: 6/27/08 **Date of Submission: 4/26/07, 3/14/08 & 6/18/08**

Primary Reviewer: Chan Park **Date:**

Team Leader: Lillie Golson **Date:**

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cc:

ANDA: 77-449
DUP/DIVISION FILE
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chan Park
7/2/2008 03:53:18 PM
LABELING REVIEWER

Lillie Golson
7/2/2008 07:28:08 PM
LABELING REVIEWER

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-449 Date of Submission: August 26, 2008

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

BLISTER - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

Satisfactory in FPL as of the 8/26/08 submission

CARTON LABELING - 5 Systems

Satisfactory in FPL as of the 8/26/08 submission

UNIT BACKING

Satisfactory in FPL as of the **4/26/07** (vol.11.1) submission (Hard copies)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of the 8/26/08 submission

MEDICATION GUIDE/INSTRUCTIONS FOR APPLYING F.T.S.

Satisfactory in FPL as of the 8/26/08 submission

REVISIONS NEEDED POST-APPROVAL:

1. The sponsor did not submit the labeling in SPL.

2. Medication Guide - May delete the text "[See USP controlled Room Temperature" associated with the CRT.

NOTE TO CHEMIST

1. The sponsor's drug product system is different from that of the RLD.

2. Please note that the sponsor's drug product contains 2.76 mg, 5.52 mg, 8.28 mg, and 11.04 mg fentanyl whereas the Duragesic® patch contains 2.5 mg, 5 mg, 7.5 mg, & 10 mg fentanyl, respectively.

3. The sponsor's drug products do not contain "alcohol", whereas the innovator 's does. In addition, the sponsor's system is a Matrix system as opposed to the Reservoir system of the innovator's.

4. The sponsor stated that the ink used on the backing of the patch does not leach through to the system. They submitted supporting data to verify their statement. Is their statement accurate?

FOR THE RECORD:

1. MODEL LABELING - Duragesic® Patch (NDA 19-813/S-033), approved 2/7/08.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2895 (Volume B.1.2).

4. PATENTS/EXCLUSIVITIES

   All patents and exclusivities are expired.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISONS

   RLD - Do not store above 77°F (25°C).

   ANDA - Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature]

6. PACKAGING CONFIGURATIONS

   RLD - 5s of 12.5 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

   ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

7. CONTAINER/CLOSURE

   P. 4450, B.1.2
   (b) (4) pouchstock and material and (b) (4) tray. The (b) (4) pouchstock is the same material approved in Aveva Drug Delivery System's Nicotine Transdermal systems (NDA 19-983). It is CRC.

8. This drug product is being manufactured by Aveva Drug Delivery System, Inc.

9. The ink used for the backing unit is the same one used for the approved NDA 19-983 (Nicotine Transdermal System). (vol. 5.1)

10. Regarding the comment on adding "a" in association with the fentanyl TDS in the pharmacokinetics subsection, see e-mail below:

From: Golson, Lillie D
Sent: Sunday, March 26, 2006 3:35 PM
To: Park, Chan H
Cc: Conner, Dale P; Golson, Lillie D; Rickman, William P; Sanchez, Aida L
Subject: FW: Control Doc.- fentanyl patches

Hi Chan,

I spoke with Dale about ways we could more accurately reflect the information in the title of the tables and charts of the pK section of the Clinical Pharmacology for the fentanyl patches to show that the data came from a product other than the ANDA holders. In discussing with John, we decided that adding the word "a" before fentanyl transdermal system in the two titles where "Duragesic" currently appears is the simplest way to address this. The labeling remains basically "the same as..." and reflects that the study was done on "a" system, not necessarily the ANDAs. I would recommend that we make the same change in the other fentanyl applications.

Thanks Dale for your input. Lillie

11. The overlay study the sponsor submitted 6/3/08 is under review by the Bio division.

12. The revised labeling submitted 6/18/08 includes information associated with the overlay study with Bioclusive™ overlay. The study was found acceptable by the Bio Div.

From: Dhariwal, Kuldeep R
Sent: Thursday, October 09, 2008 8:20 AM

To: Suh, Keri Ahn; Park, Chan H; Nair, Anil K
Cc: Dhariwal, Kuldeep R
Subject: RE: 77-449 (Fentanyl T.S. from Teva)

Chan:

The overlay study is acceptable. Anil Nair's review was signed on 8/9/2008 by the DBE 2 Director and is in the DFS. The firm used Bioclusive transparent dressing manufactured by Johnson and Johnson. Kuldeep

13. The sponsor proposed blister package as opposed to the innovator's pouch, hence all the information is printed one side. We expressed a concern that the text on your proposed blister appears too cluttered leading to a potential medication error. In response to this concern, the sponsor expanded the printing area of the blister by adding more printable flange to the blister as demonstrated by the blank samples submitted 8/26/08. It should be notes that the blank sample blister for 25 mcg/hr submitted 8/26/08 does not reflect the expanded one, rather the original one as indicated by the sponsor. The sponsor claimed that the new one has expanded printing space that is of comparable size to the 50 mcg/hr. The sponsor claimed that their proposal does not appear more cluttered than the innovator's after the extension. We will accept the proposal.

14. The sponsor included in the submission of 8/26/08 several potential advantages of their proposed blister packaging over the innovator's pouch in terms of safety concern and storage.

15. As claimed by the sponsor, it appears that the sponsor's blister configuration poses less risk of inadvertent damaging of the patch while opening the packaging than the innovator's pouch.

16. The name and strengths appearing on the unit backing is in accordance with the color scheme employed by the RLD. The prominence and legibility of the sponsor's drug identification (name and strength) is comparable to those of the RLD. We will find this acceptable.

17. We will not ask the sponsor to submit the REMS proposal until the innovator's REMS is found acceptable by the Agency. See e-mail below from Peter. It appears that the innovator's REMS has not been approved by the Agency.

From: Rickman, William P
Sent: Tuesday, October 07, 2008 8:53 AM
To: Golson, Lillie D
Subject: RE: Provigil (modafinil) RE: 20-717/S-020

We don't have to wait for the REMS to be approved for the RLD before we can approve a generic. If at the time of approval of a generic, and the RLD doesn't have a REMS approved and in place, I think we can go ahead and approve a generic with language in the AP letter saying if a REMS is approved for the innovator they will have to submit one also. This is standard language in all of our AP letters. We are taking this approach with the upcoming fentanyl TDS approval. Peter

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Date of Review: 10/9/08 **Date of Submission: 8/26/08**

Primary Reviewer: Chan Park **Date:**

Team Leader: Lillie Golson **Date:**

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cc:
ANDA: 77-449
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Review

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

/s/

Chan Park
10/14/2008 03:41:12 PM
LABELING REVIEWER

Lillie Golson
10/14/2008 05:55:08 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

CHEMISTRY REVIEWS

ANDA #77-449

Fentanyl Transdermal System, 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 77-449

2. REVIEW #: 1

3. REVIEW DATE: October 25, 2005

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	December 17, 2004
Minor Amendment	March 21, June 13, 2005
BP/Innovene Correspondence	June 15, 2005
Amendment	April 20, 2005 ⓔ 11/25/05

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-8642
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Fentanyl Transdermal System

9. LEGAL BASIS FOR SUBMISSION:
The basis for TEVA's proposed ANDA for Fentanyl Transdermal System, 25, 50, 75, 100 µg/h is the approved reference listed drug Duragesic (NDA 19-813) marketed by Alza. The firm has filed Paragraph III certification for U.S. Patent No. 4588580 which expired on July 23, 2004 and was extended to January 23, 2005 for pediatric exclusivity. TEVA also acknowledges that there is a new exclusivity for a New Patient Population (NPP) with Pediatric Extension to November 20, 2006. TEVA states that they will not label the product for that patient population until after the expiration of the exclusivity.

10. PHARMACOLOLOGICAL CATEGORY: Management of chronic pain

11. DOSAGE FORM: Transdermal system

12. STRENGTH/POTENCY: 25, 50, 75, 100 µg/h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

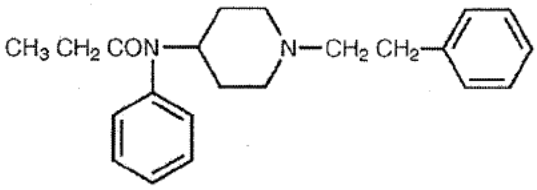
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
N-(1-Phenethyl-4-piperidyl)propionanilide
Molecular Formula: $C_{22}H_{28}N_2O$
Molecular Weight: 336.5

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	Jan 5, 2005	Reviewed by J. Boal
	IV			1	Inadequate	Oct 19, 2005	
	III			1	Adequate	Oct 23, 2005	
	III			1	Adequate	Oct 25, 2005	Information Request
	III			1	Adequate	Oct 24, 2005	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Deficient	9/13/05	C. Park
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		
Clinical (Skin Irritation)	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 77-449

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Fentanyl (b) (4) is described as (b) (4) (b) (4) It is a potent opioid analgesic and is a Schedule II controlled substance.

The drug product is non-compendial. The drug product is a drug in adhesive matrix manufactured by (b) (4)

Four different strengths are manufactured: 25 µg/h (10.7 cm^2), 50 µg/h (21.4 cm^2), 75 µg/h (32.1 cm^2) and 100 µg/h (42.8 cm^2).

It should be noted that the systems contain 10% more drug than the corresponding RLD and are 7% larger in size.

B. Description of How the Drug Product is Intended to be Used

A new patch is applied to the skin every three days. The old patch should be removed and disposed of in an appropriate manner (see labeling).

C. Basis for Approvability or Not-Approval Recommendation
Firm needs to resolve issues concerning specifications, analytical methods, stability commitment and other deficiencies as noted in the deficiency letter.

III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/Chemist/10/25/05
HFD-647/GJSmith/Team Leader/
HFD-615/TPalat/Project Manager/

C. CC Block

ANDA 77-449
DIV FILE
Field Copy

Following this page, 11 pages withheld in full - (b)(4)

Comment: Please provide the (b) (4) (b) (4) **or explain the same.**

Comment: Please provide updated stability data for the exhibit batches.

30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Deficient, 9/13/05

33. ESTABLISHMENT INSPECTION

Pending.

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement to prepare an Environmental Assessment or Environmental Impact Statement is requested in accord with 21 CFR 25.31(a).

Following this page, 2 pages withheld in full - (b)(4)

2. The labeling, bioequivalence and clinical (skin irritation and wear studies) portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-449
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/10/25/05 11/9/05
HFD-647/GJSmith/ 11/8/05
HFD-615/TPalat/ 11/14/05

F/T by: rad11/8/05
V:\FIRMSAM\TEVA\LTRS&REV\77449R1

ANDA #77-449

Fentanyl Transdermal System, 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 77-449

2. REVIEW #: 3 Chemistry Review #2 was not located.

3. REVIEW DATE: September 14, 2007

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	December 17, 2004
Minor Amendment	March 21, June 13, 2005
BP/Innovene Correspondence	June 15, 2005
Minor Amendment	February 24, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	January 3, 2007
Minor Amendment	April 3, 2007
Minor Amendment	April 16, 2007
Telephone Amendment	April 24, 2007
Minor Amendment	May 3, 2007
Minor Amendment	July 27, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-8642

Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Fentanyl Transdermal System

9. LEGAL BASIS FOR SUBMISSION:
The basis for TEVA's proposed ANDA for Fentanyl Transdermal System, 25, 50, 75, 100 µg/h is the approved reference listed drug Duragesic (NDA 19-813) marketed by Alza. The firm has filed Paragraph III certification for U.S. Patent No. 4588580 which expired on July 23, 2004 and was extended to January 23, 2005 for pediatric exclusivity. TEVA also acknowledges that there is a new exclusivity for a New Patient Population (NPP) with Pediatric Extension to November 20, 2006. TEVA states that they will not label the product for that patient population until after the expiration of the exclusivity.

10. PHARMACOLOLOGICAL CATEGORY: Management of chronic pain

11. DOSAGE FORM: Transdermal system

12. STRENGTH/POTENCY: 25, 50, 75, 100 µg/h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__Rx ___OTC

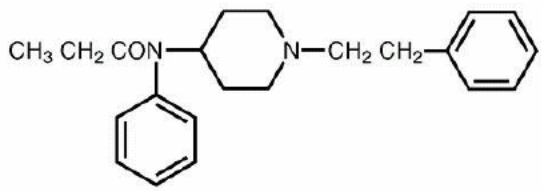
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
N-(1-Phenethyl-4-piperidyl)propionanilide
Molecular Formula: $C_{22}H_{28}N_2O$
Molecular Weight: 336.5
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	Apr 4, 2007	Reviewed by D. Klein
	IV			1	Adequate	Jun 12, 2005	
	III			1	Adequate	Oct 23, 2005	
	III			1	Adequate	Jun 12, 2005	
	III			1	Adequate	Oct 24, 2005	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Deficient	9/13/05	C. Park
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		
Clinical (Skin Irritation)	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 77-449

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Fentanyl (b) (4) is described as (b) (4) (b) (4). It is a potent opioid analgesic and is a Schedule II controlled substance.

The drug product is non-compendial. The drug product is a drug in adhesive matrix manufactured by (b) (4).

Four different strengths are manufactured: 25 µg/h (10.7 cm), 50 µg/h (21.4 cm), 75 µg/h (32.1 cm^2) and 100 µg/h (42.8 cm^2).

It should be noted that the systems contain 10% more drug than the corresponding RLD and are 7% larger in size.

B. Description of How the Drug Product is Intended to be Used

A new patch is applied to the skin every three days. The old patch should be removed and disposed of in an appropriate manner (see labeling).

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved.

Following this page, 15 pages withheld in full - (b)(4)

Response: (b) (4) [redacted] **results were reported.**

Comment: Please provide updated stability data for the exhibit batches.

Response: Updated stability data up to 12 months are provided in Attachment 17. (b) (4) [redacted].

30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Deficient, 9/13/05

33. ESTABLISHMENT INSPECTION

Pending.

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement to prepare an Environmental Assessment or Environmental Impact Statement is requested in accord with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: None

cc: ANDA 77-449
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/9/14/07
HFD-647/GJSmith/
HFD-615/LLongstaff/

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-449 APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT:

The deficiencies presented below represent MINOR deficiencies.

1. We acknowledge your commitment to develop and validate methods for the testing of [redacted] (b) (4), to generate the appropriate specifications and submit the information as soon as it becomes available. Please submit the methods, test results and specifications for [redacted] (b) (4) prior to approval.

2. Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. You are referred to the letter posted on the Office of Generic Drugs website. The following data package should be submitted:

   For each excipient in the formulation:
   - manufacturer's COA including solvents
   - applicant's updated COA for the excipient including solvent specification (solvent identity, acceptance criteria and analytical method). Loss on drying would be acceptable if only Class 3 solvent/s is used in the manufacture of an ingredient
   - applicant's test data for solvents, including data for class 3 solvents, should be submitted for the excipients
   - method validation data if non-USP methods are used
   - applicant must demonstrate that the excipient meets ICH Q3C option 1 or option 2

   The finished product specification should be updated to state compliance with USP<467>.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Shanaz Read
7/16/2008 11:00:49 AM
CHEMIST

Laura Longstaff
8/11/2008 01:57:43 PM
CSO

Glen Smith
8/15/2008 08:19:36 AM
CHEMIST

ANDA #77-449

Fentanyl Transdermal System, 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 77-449

2. REVIEW #: 4

3. REVIEW DATE: September 26, 2008

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	December 17, 2004
Minor Amendment	March 21, June 13, 2005
BP/Innovene Correspondence	June 15, 2005
Minor Amendment	February 24, 2006
Minor Amendment	January 3, 2007
Minor Amendment	April 3, 2007
Minor Amendment	April 16, 2007
Telephone Amendment	April 24, 2007
Minor Amendment	May 3, 2007
Minor Amendment	July 27, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	September 18, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-8642

Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Fentanyl Transdermal System

9. LEGAL BASIS FOR SUBMISSION:
The basis for TEVA's proposed ANDA for Fentanyl Transdermal System, 25, 50, 75, 100 µg/h is the approved reference listed drug Duragesic (NDA 19-813) marketed by Alza. The firm has filed Paragraph III certification for U.S. Patent No. 4588580 which expired on July 23, 2004 and was extended to January 23, 2005 for pediatric exclusivity. TEVA also acknowledges that there is a new exclusivity for a New Patient Population (NPP) with Pediatric Extension to November 20, 2006. TEVA states that they will not label the product for that patient population until after the expiration of the exclusivity.

10. PHARMACOLOLOGICAL CATEGORY: Management of chronic pain

11. DOSAGE FORM: Transdermal system

12. STRENGTH/POTENCY: 25, 50, 75, 100 µg/h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__Rx ___OTC

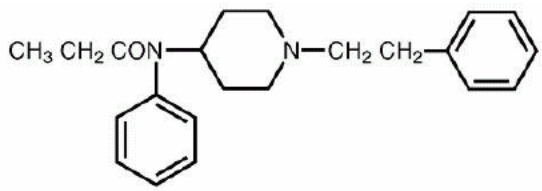
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
N-(1-Phenethyl-4-piperidyl)propionanilide
Molecular Formula: $C_{22}H_{28}N_2O$
Molecular Weight: 336.5
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	Apr 4, 2007	Reviewed by D. Klein
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	III			1	Adequate	Oct 23, 2005	
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	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	10/8/08	Shawnte Adams
Methods Validation	NA		
Labeling	Deficient	7/2/08	C. Park
Bioequivalence	Acceptable	8/9/08	Aril K. Nair
EA	NA		
Radiopharmaceutical	NA		
Clinical (Skin Irritation)	Acceptable	9/26/08	B. Davit

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 77-449

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Fentanyl (b) (4) is described as (b) (4) (b) (4). It is a potent opioid analgesic and is a Schedule II controlled substance.

The drug product is non-compendial. The drug product is a drug in adhesive matrix manufactured by (b) (4)

Four different strengths are manufactured: 25 µg/h (10.7 cm), 50 µg/h (21.4 cm), 75 µg/h (32.1 cm^2) and 100 µg/h (42.8 cm^2).

It should be noted that the systems contain 10% more drug than the corresponding RLD and are 7% larger in size.

B. Description of How the Drug Product is Intended to be Used

A new patch is applied to the skin every three days. The old patch should be removed and disposed of in an appropriate manner (see labeling).

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved.

Following this page, 17 pages withheld in full - (b)(4)

Response: Updated stability data up to 12 months are provided in Attachment 17.

(b) (4)

30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Deficient, 9/13/05

33. ESTABLISHMENT INSPECTION

Pending.

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement to prepare an Environmental Assessment or Environmental Impact Statement is requested in accord with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: None

cc: ANDA 77-449
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/9/26/08
HFD-647/GJSmith/
HFD-615/

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

/s/

Shanaz Read
10/20/2008 11:54:45 AM
CHEMIST

Glen Smith
10/22/2008 09:55:39 AM
CHEMIST

Laura Longstaff
10/22/2008 04:13:52 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-449
Drug Product Name	Fentanyl Transdermal System
Strength	25 µg/hour, 50 µg/hour, 75 µg/hour, and 100 µg/hour
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454
Submission Date(s)	~~Dec. 17, 2004~~ 3/21/05
Amendment Date(s)	NA
Reviewer	Xiaojian Jiang, Ph.D.
First Generic	**No**
File Location	V:\firmsnz\TEVA\ltrs&rev\77449N1204

XJ.

Executive Summary

The firm submitted a transdermal system bioequivalence (BE) study comparing its test product, Fentanyl Transdermal System, 25 µg/hr to the reference listed drug (RLD), Duragesic® Transdermal System, 25 µg/hr (Alza Corporation). Additionally, the firm has submitted comparative *in vitro* dissolution data for the test and reference products.

The design for the BE study is a two-way, crossover study in healthy male and female subjects (n=31). For the BE study, fentanyl results (point estimate, 90% CI) are: $lnAUC_{inf}$ of 0.89, 84.34-94.16%; lnAUC0-t of 0.90, 85.08 – 95.41%; and lnCmax of 0.86, 80.54 – 92.56%. However, the study is incomplete due to deficiencies related to the analytical method validation, pharmacokinetic and statistical data reports.

The dissolution testing is incomplete because the firm didn't provide the following information: 1) the methods that were used in multimedia dissolution testing; 2) the raw data for individual dosage units; 3) the proposed dissolution method and specification (details are given in the deficiency section).

The 25-, 50-, 75-, and 100-µg/hr transdermal systems are proportionally formulated. The waivers of *in vivo* bioequivalence requirements for the 50-, 75-, and 100-µg/hr transdermal systems are pending an acceptable response to the deficiencies. The application is **incomplete**.

Note: This application also contains two additional studies (21-day Cumulative irritation study#770-0407-01 and sensitization study# 770-0407-03). These studies will be reviewed separately by an OGD Medical Officer.

Table of Contents

Submission Summary

A. Drug Product Information

Test Product	Fentanyl Transdermal System, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
Reference Product	Duragesic® Transdermal System, 25 µg/hr (also available as 12.5 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
RLD Manufacturer	Alza Corporation (Jansseen Pharmaceutical Products, LP is the U.S. distributor)
NDA No.	19-813
RLD Approval Date	8/07/1990 for 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr 2/04/2005 for the 12.5 µg/hr.
Indication	Indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN (as-needed) dosing with short-acting opioids.

B. PK/PD Information

Bioavailability	No information available
Tmax	Peak serum concentrations of fentanyl generally occur between 24 and 72 hours
Metabolism	Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug.
Excretion	Approximately 75% of the dose is excreted in urine, mostly as metabolites, with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.
Half-life	17 hours
Relevant OGD or DBE History	The Division of Bioequivalence (DBE) has received the following ANDAs for Fentanyl Transdermal system. They are listed as follows:

76-258 (Mylan, 10/12/01): approved on Jan. 28, 2005 and listed in the current orange book.
76-709 (Watson, 03/31/03): approved on Jan. 30, 2006

(b) (4)

77-051 (Levipharm,1/21/04);
77-062 (Abrika, 02/9/04);
77-154 (Tyco Hlthcare, 05/21/04):
77-449 (Teva,11/17/04): current application

(b) (4)

77-775 (Hisamitsu Pharma): pending review

The DBE also reviewed several protocols and control documents [protocols (P-99-003, P-00-012, P-03-009, P-03-063, P-04-153) and control documents (C-00-346, C-00-036, C-01-122, C-01-175, C-01-550, C-02-490, C-02-134, C-02-568, C-03-073, C-03-226, C-03-344, C-03-467)].

DBE recommendations to establish bioequivalence:

The DBE recommends a single-dose fasting in vivo bioequivalence study on the lowest strength (25 µg/hr), with bioequivalence assessment based on the parent compound, fentanyl. The higher strengths are eligible for biowaivers (based on an acceptable BE study on the 25-µg/hr strength, acceptable in vitro release testing, and proportional similarity). A skin irritation/sensitization study is also recommended on a placebo patch that has all of the inactive ingredients and is identical to the proposed product in every manner except for the absence of fentanyl. The duration of the BE study should be 72 hours. A naltrexone blockade should be administered. As stated in the review of C-00-012, the decision to use the lowest strength was based on the OGD Medical Officer's (Dr. Mary Fanning) recommendation. In the current Orange Book (current through 1/2005), the 25 µg/hr strength is the RLD.

The DBE recommends comparative in vitro release testing be conducted on 12 dosage units of each strength using the following conditions:

(1) Several different media (water, 0.1 N HCl, and pH 4.5, 6.8, and 7.5 buffers) and a discriminating agitation speed should be used to obtain multipoint dissolution profiles. A surfactant may be used with appropriate justification. Recommendations for sampling times are provided in USP 28 <711> and <724>.
(2) Additional dissolution testing should be conducted as follows:

Media: 600 ml of 0.1M phosphate buffer, pH 3.5
Apparatus: USP Apparatus 5
Speed: 50 rpm
Sampling times: 0.5, 1, 2, and 8 hours or until 80% of the labeled drug content is dissolved.

Drug Specific Issues (if any) None

Agency Guidance Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (Issued 12/1999, Posted 2/3/2000 withdrawn January 31, 2005).

Application Specific Issue (if any) The following boxed warning appears in the current Duragesic® product labeling:
Because serious or life-threatening hypoventilation could occur, Duragesic® (fentanyl transdermal system) is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)

- in the management of mild pain
- in the management of intermittent pain [e.g., use on an as needed basis (prn)]
- in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment
- in patients who have acute or severe bronchial asthma

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-----
Single-dose fed	No	-----
Steady-state	No	-----
Transdermal system	Yes	1
In vitro dissolution	Yes	4
Waiver requests	Yes	3
BCS Waivers	No	-----
Vasoconstrictor Studies	No	-----
Clinical Endpoints	No	-----
Failed Studies	No	-----
Amendments	No	-----
CTD Summary Tablets	**No**	**The firm did not submit any CTD tables**

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Fentanyl
Internal Standard	(b) (4)
Method description	LC/MS/MS
QC range (pg/ml)	25, 75, 400 pg/ml
Standard curve range (pg/ml)	10.0 to 500 pg/ml
Limit of quantitation (pg/ml)	10.0 pg/ml
Average recovery of Drug (%)	70.4
Average Recovery of Int. Std (%)	Not reported (it is expected to be similar as Fentanyl)
QC Intraday precision range (%)	2.97-5.08
QC Intraday accuracy range (%)	99.716-102.99
QC Interday precision range (%)	2.76-3.94
QC Interday accuracy range (%)	100.485-101.47
Bench-top stability (hrs)	**Not reported**
Stock stability (days)	27 days at -5°C in 50:50 methanol: water and 1.0 ml/l glacial acetic acid. 27 days at -20°C in methanol.
Processed stability (hrs)	72 at RT
Freeze-thaw stability (cycles)	3 at -20°C
Long-term storage stability (days)	509 days at -20°C
Dilution integrity	**Not reported.**
Specificity	Yes
SOPs submitted	**No**
Bioanalytical method is acceptable	No

Comment on the analytical validation:

- The firm didn't provide the bench-top stability (short-term stability of fentanyl in matrix at room temperature) and dilution integrity data.
- The firm didn't provide the SOP dealing with analytical procedure and sample processing.

E. In Vivo Studies

1. Single-dose Bioequivalence Study

Study Summary	
Study No.	**770-0407-02**
Study Design	Randomized, Single-dose, Two-way, Crossover
No. of subjects enrolled	36
No. of subjects completing	31
No. of subjects analyzed	31
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Males: 21 Males: 10
Test product	Fentanyl Transdermal system
Reference product	Duragesic® Transdermal System
Strength tested	25µg/hr
Dose	1 X 25µg/hr over 72-hour period

Summary of Statistical Analysis, Fasting Bioequivalence Study			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		LowCI	**UppCI**
AUC∞	0.89	84.34	94.16
AUC0-t	0.90	85.08	95.41
Cmax	0.86	80.54	92.56

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays***		**Actual number**		**% of total assays***	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Concentrations >ULQ	20	48	1.40	3.37	20	48	1.40	3.37
Deleted from calculations due to retention time shift.	0	1	0	0.07	0	1	0	0.07
Total	20	49	1.40	3.44	20	49	1.40	3.44

***Total # samples assayed = 1425**

Did use of recalculated Plasma concentration data change study outcome? **No.** (no PK repeat)

F. Formulation

Location in appendix	Section I.B, Page 24
Are inactive ingredients within IIG limits?	See comments below
If no, list ingredients outside of limits	
If a tablet, is the product scored?	NA
If yes, which strengths are scored?	NA
Is scoring of RLD the same as test?	NA
Is the formulation acceptable?	Pending pharm/tox consultation results
If not acceptable, why?	NA

Comments on the Formulation:

Two inactive ingredients, Polyisobutene Adhesive and Polybutene (b) (4) were above the IIG limits and not listed in the IIG, respectively (see regulatory support branch check list). The Pharm/tox data submitted by the firm for both ingredients has been sent on consultation on 6/22/05. The consultation review was not yet found in the V drive.

77449.CHK.doc 77449-toxconsult-23June2005.DOC

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	See comments#1 below
Volume (mL)	
USP Apparatus type	
Rotation (rpm)	
Firm's proposed method and specification	USP Apparatus 6 (cylinders) rotating at 50 rpm with 500 mL (25 and 50 µg/h systems) or 900 mL (75 and 100 µg/h systems) of pH 6.8 Phosphate Buffer at 32 °C. 6 h: (b) (4)% 24 h: % 48 h: % 72 h: %

FDA-recommended specification	The innovator didn't use standard USP apparatus for the Duragesic® product. Therefore, the DBE has never recommended the innovator's method to other generic firms. In stead, the DBE has recommended the method that was approved for Mylan's product.
F2 metric calculated?	No
If no, reason why F2 not calculated	Pending firm's responses
Is method acceptable?	Pending satisfactory responses to deficiencies related to dissolution testing

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			

F2 metric, test compared to reference	
Strength	F2 metric
N/A	

Comments on Dissolution:

1. The DBE **didn't** previously review dissolution data for this ANDA. The firm has provided dissolution testing in six media (0.1 N HCl, Water, buffers at pH 3.4, pH 6.8, pH 4.5 and pH 7.5). However, they didn't provide the dissolution methods (apparatus, rotation speed, volume and temperature of the media) that were used for the testing. The firm also didn't provide raw data for individual dosage units, including range values (low, high), coefficient of variation, or f_2 values.

2. The firm didn't provide the proposed dissolution method and specification for quality control and stability testing of the test product in the Bio section. The reviewer found them in chemistry section (A1.12, page 4922).

3. Although the DBE has asked previous generic firms to conduct additional dissolution testing using the FDA-recommended method for Mylan's product (600 ml of 0.1M phosphate buffer at pH 3.5 using USP apparatus 5 at 50 rpm), this method was not found suitable for any of previously reviewed generic products. Therefore, due to differences in the formulation and design of the patch, this reviewer recommends not asking the firm to repeat dissolution testing using this method (see additional attachments, Table 2 for dissolution history).

4. In the firm's Standard Testing Procedure for Fentanyl drug release, the firm stated that the release data was presented as percentage of total delivered dose (µg/hr*24 hr*3), rather than percentage of labeled amount per patch. The firm is advised to clarify how the multimedia dissolution data was presented. If the percentage of total delivered dose was used, the DBE requests that the firm resubmit their data presented as percentage of labeled amount per patch for consistency.

H. Waiver Request(s)

Strengths for which waivers are requested	50 µg/hr, 75 µg/hr and 100 µg/hr
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes, The formulations are dose-proportional with respect to the area of the delivery surface and the composition of the adhesive matrix.
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	BE study and dissolution testing are both deficient.

I. Deficiency Comments

1. The firm didn't provide the bench-top stability (short-term stability of fentanyl in matrix at room temperature) and dilution integrity data. The firm also didn't provide the SOP dealing with analytical method and sample repeats.

2. Except that the 90% confidence intervals for Ln AUCt, LnAUCinf and LnCmax were provided in the integrated study report, the firm didn't provide a comprehensive pharmacokinetic and statistical report for this study. The firm should provide mean, standard deviation, coefficient of variation and Test/Reference ratios for all derived pharmacokinetic parameters (AUCt, AUCinf, Cmax, Tmax, T1/2 and Kel) and for plasma concentration at each scheduled sampling time, in a tabulated format, and SAS Analyses of Variance results.

3. The firm didn't provide the dissolution methods (apparatus, rotation speed, volume and temperature of the media) that were used in their multimedia dissolution testing. The firm also didn't provide raw data for individual units, including range values (low, high), coefficient of variation (%CV), or f_2 values. Additionally, the firm didn't provide the proposed dissolution method and specification for quality control and stability testing of the test product in the bio-section of this application.

4. In the firm's Standard Testing Procedure for Fentanyl drug release, the firm stated that the release data was presented as percentage of total delivered dose (µg/hr*24 hr*3), rather than percentage of labeled amount per patch. The firm is advised to clarify how the multimedia dissolution data was presented. If percentage of total delivered dose was used, the DBE requests the firm resubmit their data presented as percentage of labeled amount per patch for consistency.

5. Information from the firm supporting safety of the adhesives has been forwarded for a Pharm/Tox review. The results are pending.

J. Recommendations

1. The transdermal system bioequivalence study conducted by Teva on its Fentanyl Transdermal System, 25 µg/hr, lot #77082, comparing it to Alza Corporation's Duragesic® Transdermal System, 25 µg/hr, lot #0323963, is incomplete due to Deficiency Comments #1-2.

2. The dissolution testing is incomplete due to Deficiency Comments#3-4.

3. The formulations of the 50-, 75-, and 100-µg/hr strengths are proportionally similar to the 25-µg/hr strength of the test product which underwent in vivo bioequivalence testing. The waiver requests for the 50-, 75-, and 100-µg/hr strengths, however, cannot be granted at this time because the application is incomplete.

With its response, the firm should propose a dissolution method and specifications for the proposed test product.

The firm should be informed of the deficiency comments and recommendations.

The application is incomplete pending satisfactory responses to deficiency comments

JIANG Xiaojian 3/30/06

Xiaojian Jiang, Ph.D. Date Signed
Review Branch II

3/30/2006

Shriniwas Nerurkar, Ph.D. Date Signed
Team Leader, Review Branch II

4/3/06

Dale P. Conner, Pharm. D. Date Signed
Director, Division of Bioequivalence
Office of Generic Drugs

Appendix

A. Individual Study Reviews

1. Transdermal System Bioequivalence Study

a) Study Design

Study Information	
Study Number	**770-0407-02**
Study Title	A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 mcg/hr) Compared to Duragesic® (Fentanyl Transdermal System) 25 mcg/hr Patches
Clinical Site	Novum Pharmaceutical Research Services, 5900 Penn Avenue, Pittsburgh, PA 15206
Principal Investigator	Shirley Kennedy, M.D.
Study/Dosing Dates	Period 1: 07/23/04 Period 2: 08/06/04
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	Aug. 25, 2004 –Sep.20, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	60 days

Treatment ID	**A**	**B**
Test or Reference	**Test Product**	**Reference Product**
Product Name	Fentanyl Transdermal system	Duragesic® Transdermal System
Manufacturer	Teva pharmaceuticals USA (manufactured by Aveva Drug Delivery Systems, Inc in Miramar, FL for Teva).	Alza Corporation
Batch/Lot No.	77082*	0323963
Manufacture Date	06/04	N/A
Expiration Date	N/A	09/05
Strength	25 µg/hr	25 µg/hr
Dosage Form	Transdermal system	Transdermal system
Batch Size	(b) (4) units	N/A
Production Batch Size	(b) (4) batch size	N/A
Potency	97.8%	99.9%

* On pages 2955 and 3420, Volume# A1.7 and A1.8, the firm stated that lot#33938 was labeled as 77082 for the bioequivalence study.

Content Uniformity (mean, %CV)	98.0% (96.6%-100.3%, 1.3%RSD)	99.6% (96.6%-102.1, 1.6%RSD)
Formulation	See Appendix Section I.B	
Dose Administered	Single application of one 25 µg/hr patch applied to the upper arm for 72-hour interval	Single application of one 25 µg/hr patch applied to the upper arm for 72-hour interval
Patch administration and other procedures	• At Hour 0 of study Day 1 for each study period, the appropriate transdermal system was firmly placed on the prepared skin site of the upper arm and held on with the palm of the hand for approximately 30 seconds. The transdermal system remained in place for 72 hours prior to removal. During the second period, the assigned alternate treatment was applied to the alternate arm approximately at the same area. • Approximately one hour prior to application, the site was gently cleaned with warm water only and allowed to air dry, no soaps or any cleansing agents were used to clean the application site. • After the patch had been removed it was stored in a suitable container that was marked with the subject number, period, date of application and removal and treatment. At the end of the study these used patches were returned to the sponsor for analysis of remaining drug concentration. • Subjects who had sustained intolerable adverse events may be administered oral naltrexone as appropriate for the relief of symptoms as directed by the medical investigators. The continued participation of a subject who is administered naltrexone was at the discretion of the investigator. • Any subject who had the patch removed before 72 hr of application was dropped from the study and their samples were not analyzed. • Approximately 30 min and 24 hrs after the patch was removed, the site of application was reviewed by a trained and validated rater to assess the amount of any skin irritation using the same scoring system as listed in FDA Skin irritation and Sensitization Guidance. • At each vital sign measurement from 12 hr through 72 hr (12, 24, 36, 48, 60, 72) the site of application was inspected to ensure the patch was continued to adhere. The degree of adhesion was rated and recorded using the same scoring system as listed in FDA Skin irritation and Sensitization Guidance. Subject was required to avoid using soap, cleansing agents around or over the patch while it is in place or for 12 hour after removal. Subject should also avoid allowing the site of application to become excessively wet during the study.	

	• **The protocol didn't mention using tapes to hold patches during the study.**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	**A-B:** Subjects: 1, 4, 6, 7, 9, 12, 13, 16, 17, 20, 22, 23, 25, 27, 30, 32, 34, 36 **B-A:** Subjects: 2, 3, 5, 8, 10, 11, 14, 15, 18, 19, 21, 24, 26, 28, 29, 31, 33, 35
Blood Sampling Times	0, 3, 6, 12, 24, 36, 42, 48, 54, 60, 72, 74, 76, 78, 80, 82, 90, 96, 102, 108, 120, 132 and 144 hrs postdose
Blood Volume Collected/Sample	10 mL Potassium EDTA tubes
Blood Sample Processing/Storage	Blood samples were centrifuged until separation of red cells from plasma occurred. Plasma was transferred into a polypropylene tube and placed in a freezer within two hours of sample collection. The samples were stored at a temperature at or below -20° until transferred to the analytical laboratory for analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours pre-dose and 1 hours post-dose
Length of Confinement	At least 24 hours pre-dose until 144 hours post-dose.
Safety Monitoring	A health status inquiry and vital signs (sitting blood pressure, pulse rate, and respiratory rate) were obtained prior to fentanyl dosing at baseline (Hour 0), and at post-dose Hours 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 and 132 and prior to release in each study period. In addition, hematology and chemistry testing was performed in period II at 144 hrs.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects (n=31)

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	38.7
Mean	27.19	Mean	171.84	18-40	87.1	Male	67.7	Afr. Amer.	51.6
SD	8.76	SD	31.92	41-64	12.9	Female	32.3	Hispanic	3.2
Range	18	Range	125	65-75	0.0			Asian	3.2
	45		248	>75	0.0			Others	3.2

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
16	The patch (test product) fell off after 35 hr application of the patch	In period I	No
36	Tested positive for pregnancy at Period II check-in. The subject was referred to her own personal physician for follow-up and agreed to inform the clinical staff of the outcome of her physician's evaluation. The subject reported to the clinic staff that she visited her physician on 08/12/04 and subsequently terminated the pregnancy on (b) (6).	Prior to period II patch application	No
21 and 23	Tested positive for alcohol at Period II check-in	Prior to period II patch application	No
14	Withdrawn from further study participation by the investigator due to a serious adverse event that the subject experienced during the wash-out period of the study.	During the wash-out period	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Nausea	16	17
Erythema (1, minimal)*	19	9
Erythema (2, definite)	3	12
Euphoric		1
Emesis	13	10
Itchy, generalized	11	10
Light headed	1	5
Pain in the body	1	3
Headache	7	6
Tingling sensation	1	
Insect bites, bilateral lower extremities	1	
Tired	2	3
Upset stomach	1	2
Dizzy	3	3
Abdominal cramping	3	
Popping sound both ears		1
Difficulty sleeping		1
Elevated blood pressure	4	3
Decreased blood pressure		4
Tender, right lateral forearm		1
Edema		1
Ecchymosis		1
Elevated temperature	1	1
Purulence		1
Elevated WBC		1
Elevated sedimentation rate		1
Elevated C-reactive		1
Sleepy	3	1
Woozy	1	
Papules (3)	1	1
Erythema (3)	1	1
Abnormal sensation		1
Feeling high	3	3
Hot flash		1
Hot	2	
Numbness		1
Anxious	1	
flushed	1	
sleepless		1
Papules (2)		1
Total:	**100**	**110**

* irritation score

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood draw time deviations	some	some

Comments on Irritation/Adhesion/Dropouts/Adverse Events/Protocol Deviations:

Mean irritation assessments were calculated by totaling all of the irritation scores for each treatment for those subjects who completed both periods of the study and dividing this total by the number of assessments. Observed irritation scores for the subjects who completed the study ranged from a minimum score of 0 (no irritation) to a score of 3 (erythema and papules). For the 31 subjects who completed both parts of the study, the mean irritation score was **1.19** for the **test** product and **1.52** for the **reference** product, suggesting that the test product was less irritating than the reference product.

Mean adhesiveness score was calculated by adding together all of the adhesiveness scores for each treatment for all subjects who completed both periods of the study and dividing this total by the number of assessments. Observed adhesiveness scores for the subjects who completed the study ranged from a minimum score of 0 (90% adhered; essentially no lift off of the skin) to a score of 3 (<50% adhered but not detached; more than half the system lifting off of the skin but not detached). For the 31 subjects who completed both parts of the study, the mean adhesiveness score was **0.26** for the **test** product and **2.94** for the **reference** product, suggesting that the test product adhered better for the 31 subjects who completed the study. One test patch fell off 35.3 hrs after application in the first period prior to the cross-over and this subject was removed from the study and did not receive the reference product. The distribution of the adhesive scores within subjects at 72 hrs is summarized by the reviewer in the following table.

Score*	Test product (number of subjects)	Reference product (number of subjects)
0	28	13
1	5	12
2	0	4
3	0	4
4	1 (This subject removed from the study)	0
Total	34	33

* 0: ≥90% adhered (essentially no lift off the skin); 1: ≥75% to <90% adhered (some edges only lifting off the skin); 2: ≥50% to <75% adhered (less than half of the patch lifting off the skin); 3: >0% to <50% adhered but not detached (more than half of the patch lifting off the skin without falling off); 4: 0% adhered – patch detached (patch completely off the skin)

A total of 210 post-dose adverse events were reported (100 following administration of the test product and 110 following administration of the reference product). All of the reported adverse events were deemed mild to moderate with one exception. Subject 14 experienced adverse events of "tender, swollen, bruised area of the right lateral forearm" that was the result of bumping his arm on the sink during Period I confinement. This event was considered not related to the drug application. Subject# 14 was withdrawn from the study.

Several subjects experienced emesis during the study. Since this product is absorbed through skin, emesis should not affect the study integrity. Removal of these subjects is considered unnecessary.

Sampling time deviations were corrected for pharmacokinetic calculation.

The protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Fentanyl									
QC Conc. (pg/mL)	25		75	400		400 Dil 2				
Inter day Precision (%CV)	4.37		3.88	2.91		0.963				
Inter day Accuracy (%)	92.8		97.6	98.0		95.8				
Cal. Standards Conc. (ng/mL)	10.0	20.0	50.0	100	250	500				
Inter day Precision (%CV)	4.96	2.93	2.77	1.97	2.52	2.79				
Inter day Accuracy (%)	100.3	99.4	100.5	99.5	99.6	100.8				
Linearity Range(pg/ml)	10.0 to 500 pg/ml									
Range of R values	0.9969-0.9999									

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Ok, 19.35% submitted.
Were chromatograms serially or randomly selected?	Randomly, Runs# 3, 7, and 12 for Subjects# 5, 6, 13, 15, 27 and 28.

Comments on Chromatograms: Ok

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
None		

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: The study assay is incomplete due to a deficiency related to the analytical method validation.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=31)

Mean Plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	pg-hr/ml	30027.92	35.52	33424.76	31.92	0.90
AUCt	pg-hr/ml	28258.88	34.94	30984.94	29.65	0.91
Cmax	pg/ml	404.71*	36.34	460.26*	29.12	0.88
Kel	1/hr	0.02	21.59	0.02	24.91	1.04
T1/2	hr	30.86	24.20	32.63	29.06	0.95
Tmax	hr	39.61	33.60	46.97	24.53	0.84

* Ranges of individual Cmax are between 218 pg/ml to 880 pg/ml, and 238 pg/ml to 802 pg/ml for the test product and reference product, respectively.

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N= 31)

Parameter	Test	Reference	T/R	90% CI	
				LowCI	UppCI
AUC∞	28376.03	31843.29	0.89	84.34	94.16
AUCt	26714.80	29650.88	0.90	85.08	95.41
Cmax	380.11	440.25	0.86	80.54	92.56

Units: AUC=pg.hr/ml, Cmax=pg/ml

Table 10 Additional Study Information (N=31)

Root mean square error, AUC_{0-t}	0.132726
Root mean square error, AUC_{∞}	0.127539
Root mean square error, Cmax	0.161136
Ke and AUCi determined for how many subjects?	all
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:

The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnC_{max} are within the acceptable limits of 80-125%.

The firm didn't provide the arithmetic mean for pharmacokinetic parameter and plasma concentration. The reviewer's calculated values were reported. The firm also didn't provide the ANOVA SAS analysis results.

A statistically significant treatment effect was observed for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnCmax.

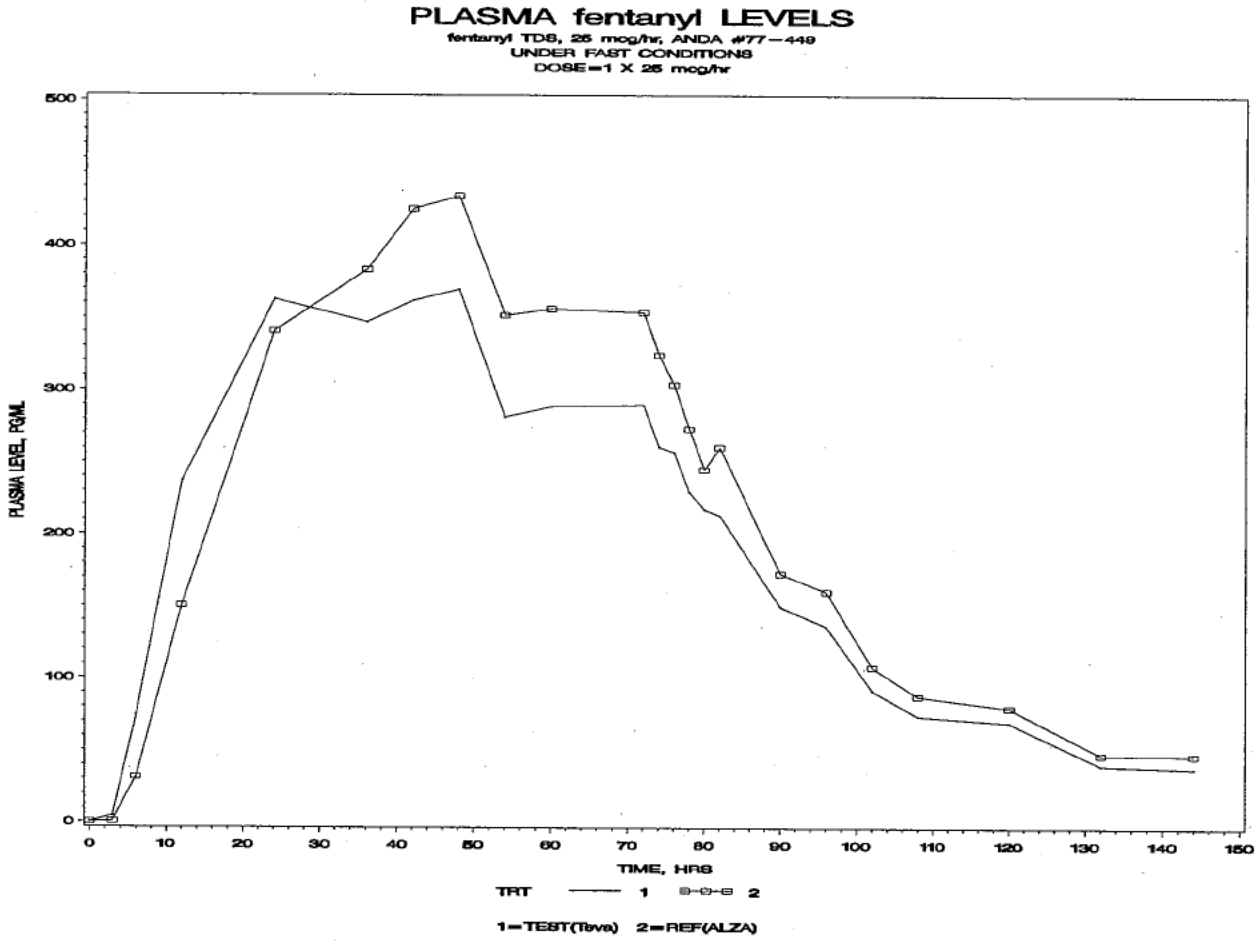
A statistically significant sequence effect was observed for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnCmax. Since this study meets the criteria for acceptance of sequence effects listed in *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence* (Jan. 2001), the observed sequence effect should not compromise the assessment of bioequivalence.

Summary and Conclusions, Transdermal System Bioequivalence Study: The study is incomplete due to deficiency comments listed in page 11.

Table 11 Mean Plasma Concentrations, Transdermal System Bioequivalence Study (unit: pg/ml)

Time (hr)	Test (n=31)		Reference (n=31)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	-	0	-	0.00
3	4.22	289.42	0.58	556.78	7.27
6	74.21	112.18	31.21	134.81	2.38
12	237.01	60.91	150.29	62.36	1.58
24	362.71	41.59	340.58	35.46	1.06
36	346.71	37.14	382.97	28.17	0.91
42	361.74	35.73	425.03	29.97	0.85
48	369.58	38.29	433.97	30.61	0.85
54	281.45	27.17	351.48	27.88	0.80
60	288.55	28.01	356.10	29.08	0.81
72	289.81	33.91	353.81	34.13	0.82
74	260.77	32.78	324.06	36.83	0.80
76	257.10	32.87	303.77	35.15	0.85
78	229.65	34.37	273.26	35.37	0.84
80	217.52	35.49	245.07	31.19	0.89
82	213.35	37.43	260.55	35.74	0.82
90	149.87	41.76	172.83	38.30	0.87
96	136.27	45.25	160.37	41.85	0.85
102	91.67	49.76	108.01	49.54	0.85
108	73.90	50.13	87.83	50.69	0.84
120	69.61	53.22	79.59	51.65	0.87
132	39.87	51.01	47.35	55.58	0.84
144	37.95	57.42	46.80	64.39	0.81

Figure 1 Mean Plasma Concentrations, Transdermal System Bioequivalence Study



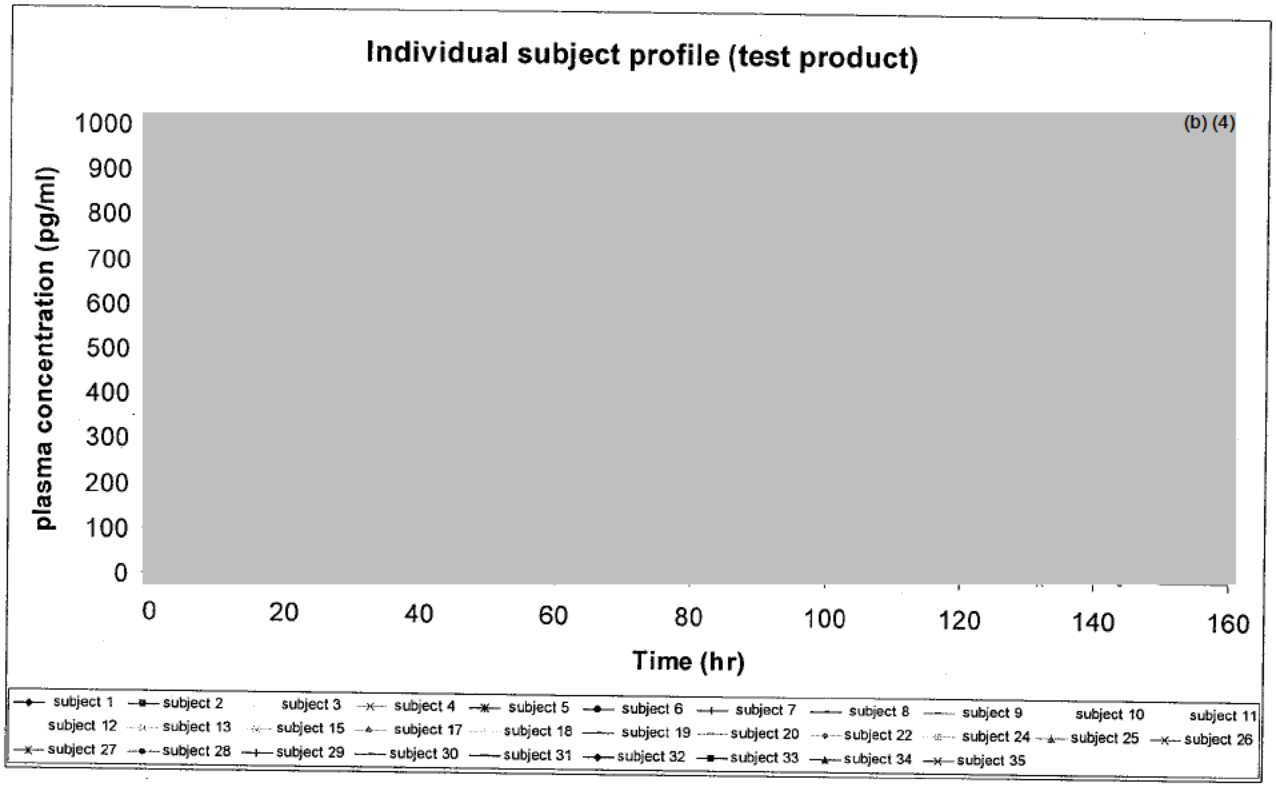
e) Analysis of transient elevations in fentanyl plasma concentration

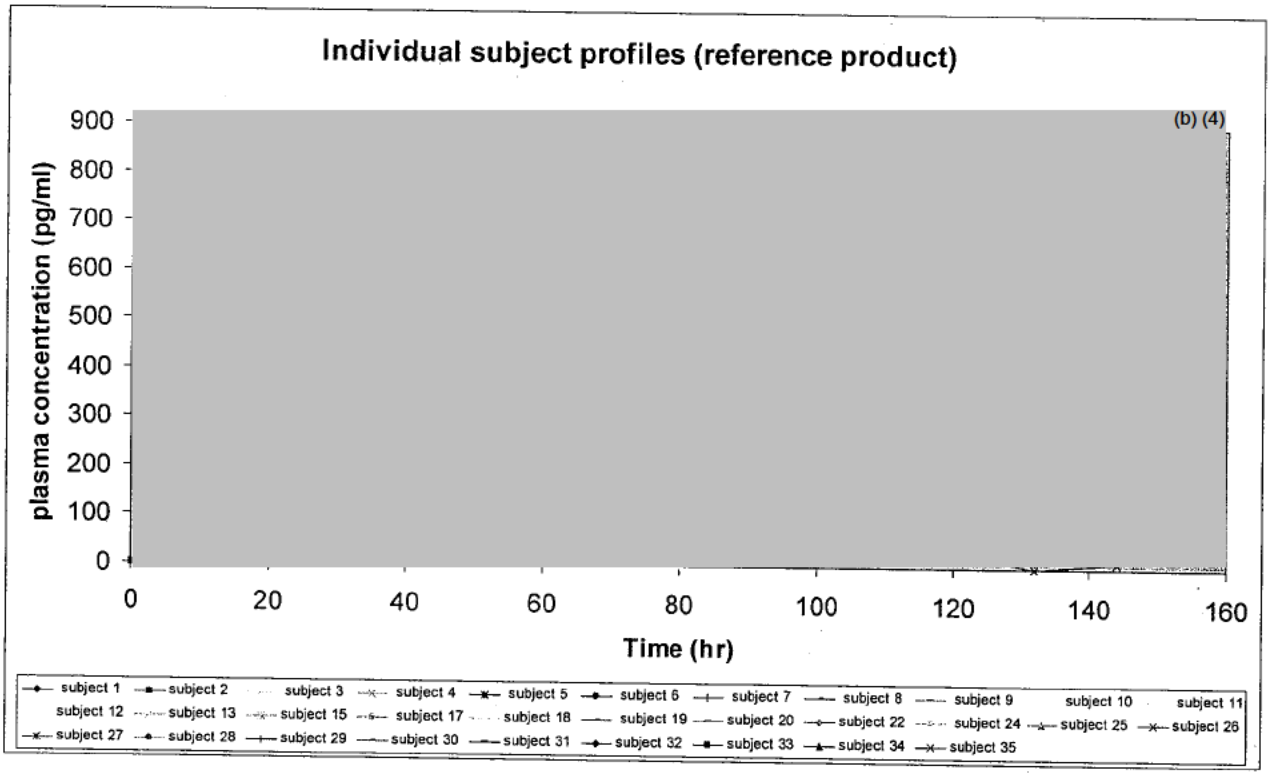
All previous ANDA reviews had examined if the transient elevations in fentanyl plasma concentrations occurred in the bioequivalence study as per Medical Officer of OGD, Dina Hixon's request. The DBE found that there may be transient elevations in plasma fentanyl concentrations from Noven and (b) (4) bioequivalence studies.

The reviewer conducted analysis for this study using the same approach used by other reviews. There are no distinct transient elevations in plasma concentration observed for both test and reference products in this study. However, subject#2 had the highest Cmax for both test and reference treatment. It is noted there are no marked increase in the intensity of adverse events for this subjects in comparison with other subjects.

Conclusion: The reviewer does not observe any transient elevations in plasma concentration or any relationship with adverse event.

Individual subject plasma profiles from this study are shown below.


Individual subject profile (test product)
(b) (4)
plasma concentration (pg/ml)
1000
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
Time (hr)
subject 1
subject 2
subject 3
subject 4
subject 5
subject 6
subject 7
subject 8
subject 9
subject 10
subject 11
subject 12
subject 13
subject 15
subject 17
subject 18
subject 19
subject 20
subject 22
subject 24
subject 25
subject 26
subject 27
subject 28
subject 29
subject 30
subject 31
subject 32
subject 33
subject 34
subject 35


Individual subject profiles (reference product)
(b) (4)
plasma concentration (pg/ml)
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
Time (hr)
subject 1
subject 2
subject 3
subject 4
subject 5
subject 6
subject 7
subject 8
subject 9
subject 10
subject 11
subject 12
subject 13
subject 15
subject 17
subject 18
subject 19
subject 20
subject 22
subject 24
subject 25
subject 26
subject 27
subject 28
subject 29
subject 30
subject 31
subject 32
subject 33
subject 34
subject 35

B. Formulation Data

1. Formulation for the Test Product (Not to be released under FOI)

Component	mg/cm^2	%w/w	10.7 cm^2 (25 µg/h)	21.4 cm^2 (50 µg/h)	32.1 cm^2 (75 µg/h)	42.8 cm^2 (100 µg/h)
			mg	mg	mg	mg
(b) (4)						

It should also be noted that the amount of fentanyl per patch is about 10.4(b)(4)% greater than in the RLD with a 7% larger patch surface area.

Dose (µg/ml)	Test product		Reference product	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	10.7	2.76 (b)(4)	10	2.5
50	21.4	5.52	20	5
75	32.1	8.28	30	7.5
100	42.8	11.04	40	10

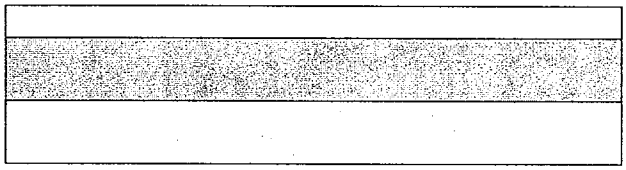
Note: (b) (4) product under ANDA (b) (4) was considered not pharmaceutically equivalent to the RLD drug because it (b) (4). Tyco Healthcare Mallinckrodt's product under ANDA 77-154 is a matrix system containing similar overage (10%) as this test product (10.4 (b)(4)%). Please see Additional Attachment, Table 1 for comparative content of the patches.

Description of the test product:

A rectangular unit with round corners consisting of an opaque tan backing imprinted as per approved artwork, laminated to an overlapping clear release liner.

Fentanyl transdermal system is a rectangular unit comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1. A BACKING LAYER OF POLYESTER FILM;
2. FENTANYL IN POLYISOBUTENE ADHESIVE MATRIX THAT CONTROLS THE RATE OF FENTANYL DELIVERY TO THE SKIN SURFACE; AND
3. A PROTECTIVE POLYESTER RELEASE LINER



The active component of the system is fentanyl. The remaining components are pharmacologically inactive.

2. Formulation for the Reference Product*(Not to be released under FOI)

Component Weight per Dosage Form (mg)

Nominal Delivery Rate Delivery Area (Size)	25 mcg/hr (10 cm²)	50 mcg/hr (20 cm²)	75 mcg/hr (30 cm²)	100 mcg/hr (40 cm²)
Component				
Occlusive Backing				
Film, Polyester/EVA	(b) (4)			
Drug Reservoir				
Fentanyl Base (Active Component)	2.5	5	7.5	10
Hydroxyethyl Cellulose, NF	(b) (4)			
Ethanol, 95%, USP				
Release Membrane				
Film, EVA	(b) (4)			
Contact Adhesive				
Silicone Adhesive	(b) (4)			
	(b) (4)			
Protective Liner				
	(b) (4)			
Total Weight:	659	1255	1810	2377 mg

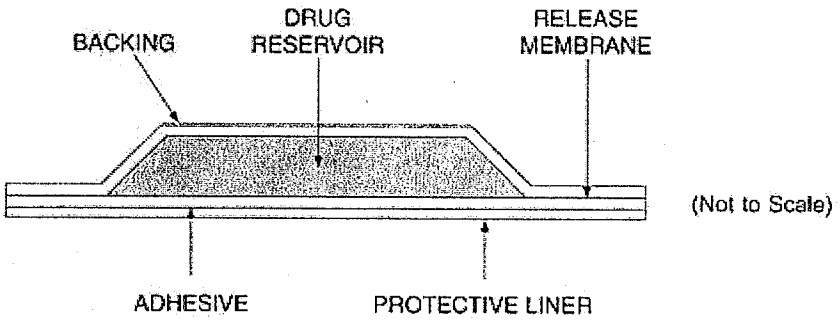
* (b) (4)

*formulation is obtained from OCPB review of NDA 19-813 dated 12/21/87.

Description of the reference product:

DURAGESIC® is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of polyester film;
2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose;
3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface;
4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive. Less than 0.2 mL of alcohol is also released from the system during use.

C. Dissolution Data

The dissolution testing on 12 units of the test and reference products of all four strengths was conducted the following media: **A: 0.1 HCl; B:pH 3.4; C: pH 4.5; D: pH 6.8; E: Water and F: pH 7.5** The dissolution data are summarized in the following tables.
Note: **The individual data, the range and %CV were not reported.**

Table 1 Comparative Dissolution testing using media----A: 0.1 N HCl.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	40			17		
6	70			27		
12	93			37		
24	112			54		
48	116			76		
72	111			93		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	38			17		
6	68			25		
12	93			38		
24	113			54		
48	119			78		
72	116			96		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	37			12		
6	69			20		
12	95			30		
24	119			49		
48	128			75		
72	128			98		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	36			13		
6	67			21		
12	95			31		
24	122			49		
48	135			78		
72	138			99		

Table 2 Comparative Dissolution testing using media----B:pH 3.4.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	52			23		
6	85			34		
12	112			47		
24	136			65		
48	149			90		
72	148			105		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	50			20		
6	84			31		
12	112			44		
24	136			64		
48	147			89		
72	148			103		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	48			16		
6	80			25		
12	107			36		
24	134			55		
48	147			81		
72	149			98		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	46			16		
6	77			25		
12	105			36		
24	132			55		
48	144			80		
72	147			98		

Table 3 Comparative Dissolution testing using media----C: pH 4.5.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	44			22		
6	77			33		
12	105			46		
24	132			65		
48	143			90		
72	143			105		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	45			20		
6	77			30		
12	105			42		
24	132			60		
48	144			85		
72	143			101		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	45			15		
6	77			25		
12	105			36		
24	132			55		
48	144			81		
72	143			99		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	44			16		
6	76			25		
12	104			36		
24	131			55		
48	142			81		
72	142			100		

Table 4 Comparative Dissolution testing using media----D: pH 6.8.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	40			23		
6	68			34		
12	94			47		
24	114			66		
48	127			92		
72	128			109		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	41			20		
6	72			32		
12	95			45		
24	118			65		
48	129			90		
72	131			105		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	40			16		
6	68			25		
12	93			37		
24	117			57		
48	130			85		
72	132			104		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	39			17		
6	67			27		
12	93			39		
24	118			58		
48	131			85		
72	134			103		

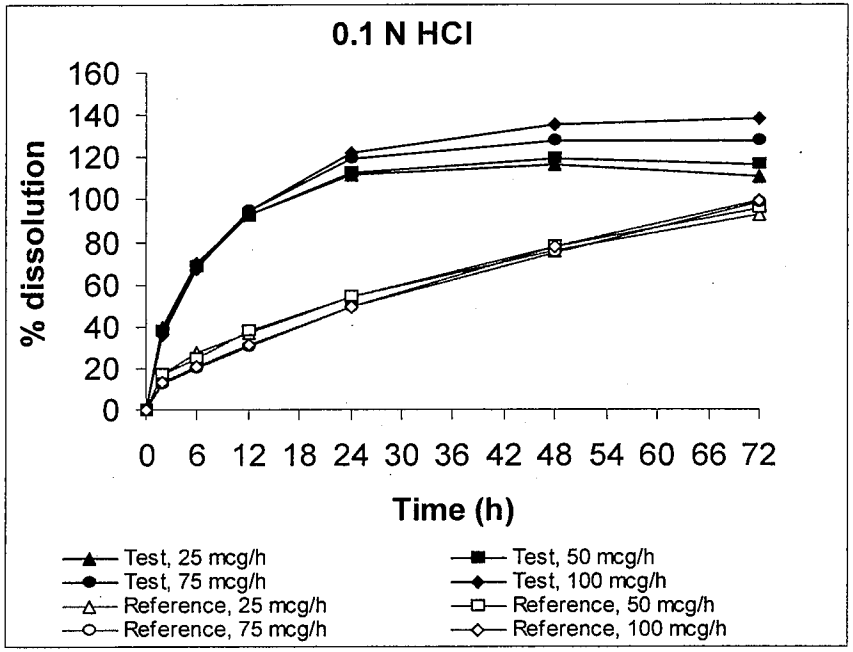
Table 5 Comparative Dissolution testing using media----D: Water.

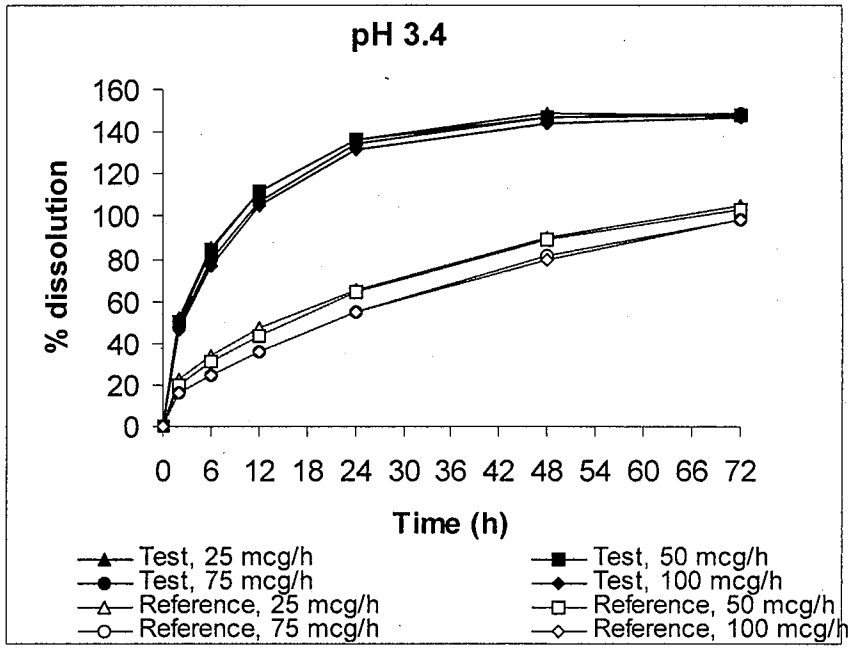
Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	49			23		
6	79			34		
12	105			47		
24	126			67		
48	134			93		
72	132			110		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	47			20		
6	77			32		
12	102			43		
24	123			62		
48	130			87		
72	132			104		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	30			16		
6	75			26		
12	101			38		
24	125			58		
48	135			87		
72	135			105		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	37			16		
6	75			25		
12	103			37		
24	129			56		
48	142			84		
72	142			104		

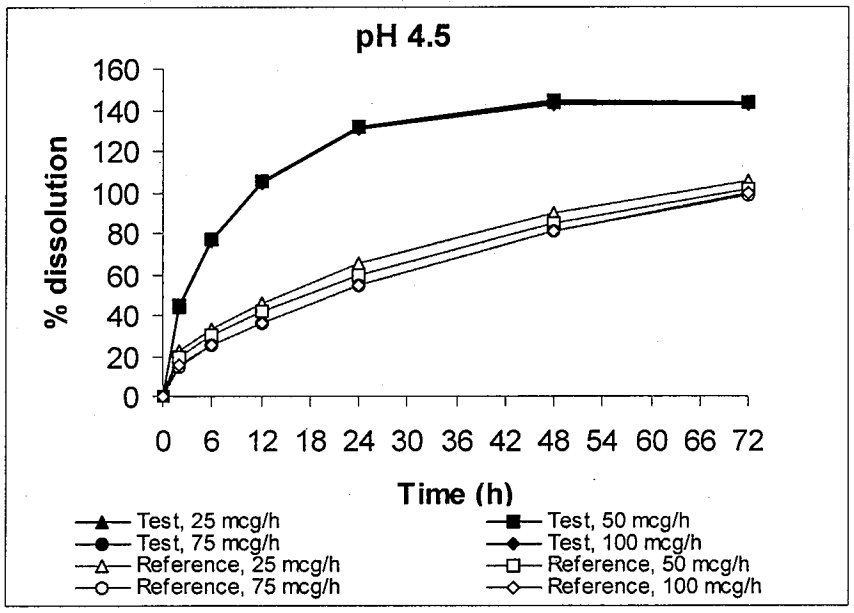
Table 6 Comparative Dissolution testing using media----D: pH 7.5.

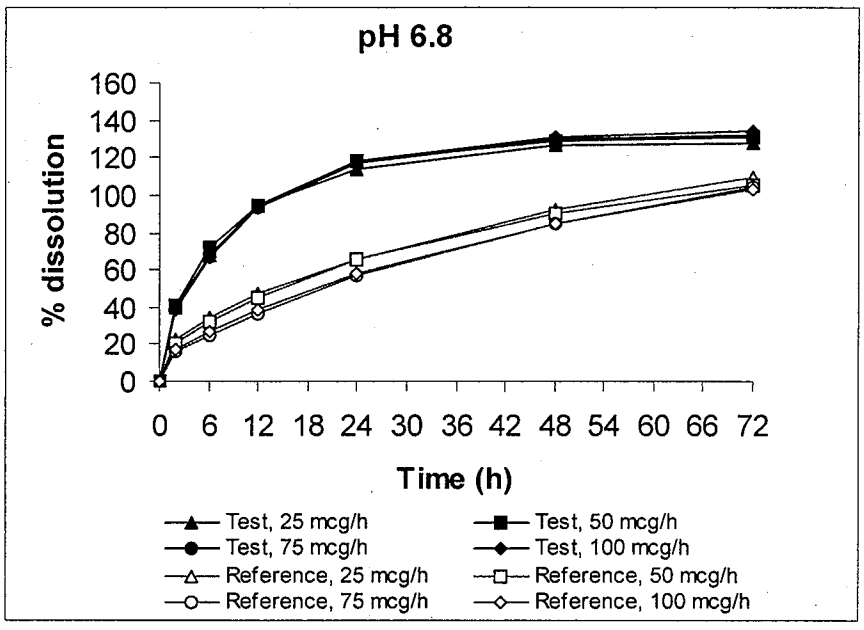
Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	40			21		
6	67			32		
12	88			42		
24	105			60		
48	109			83		
72	104			97		
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	40			17		
6	67			28		
12	89			40		
24	105			58		
48	110			82		
72	105			96		
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	41			15		
6	70			23		
12	94			35		
24	115			53		
48	124			79		
72	123			94		
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	40			15		
6	68			23		
12	93			33		
24	116			49		
48	125			74		
72	125			92		

Figure 2 Test to reference and different strengths dissolution profile comparisons in six media

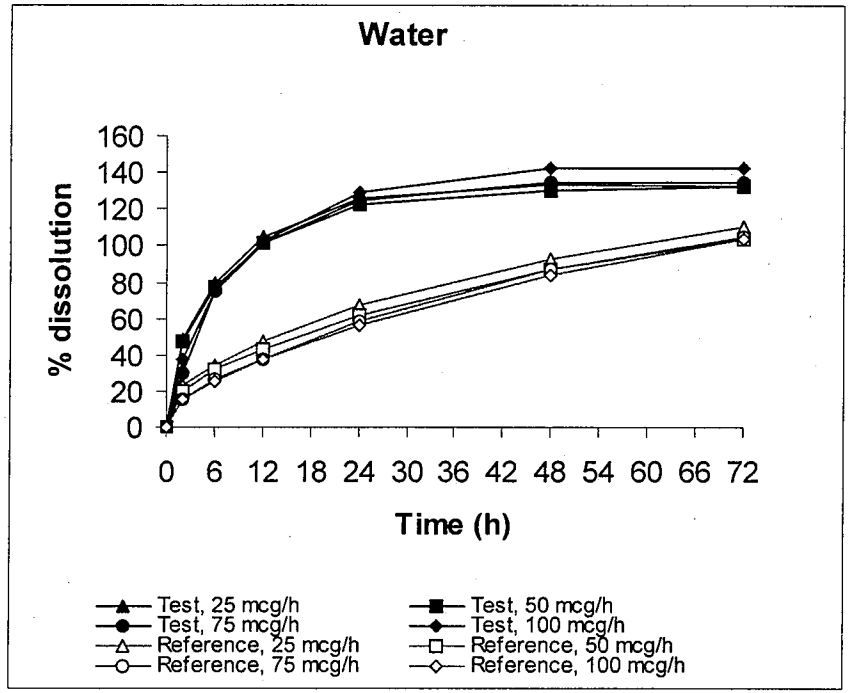








Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr



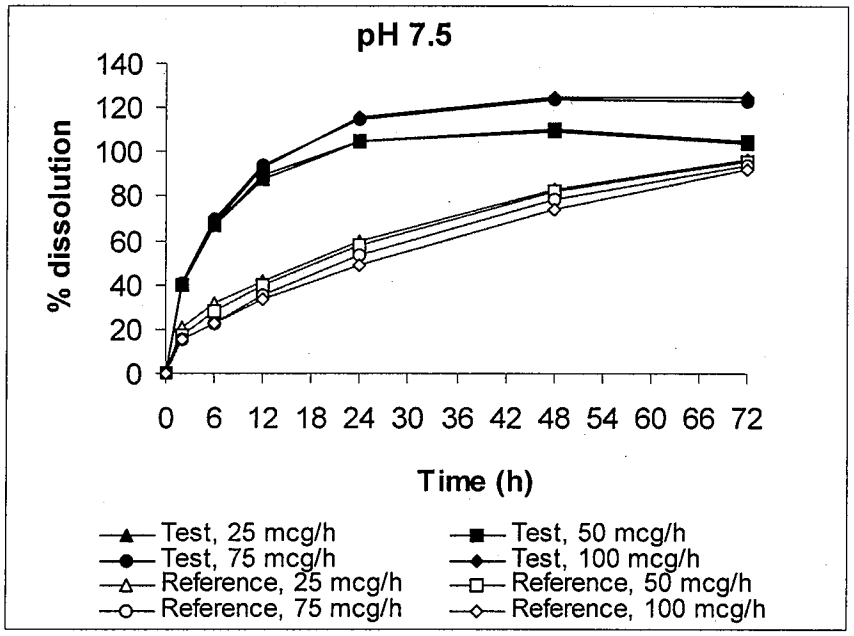
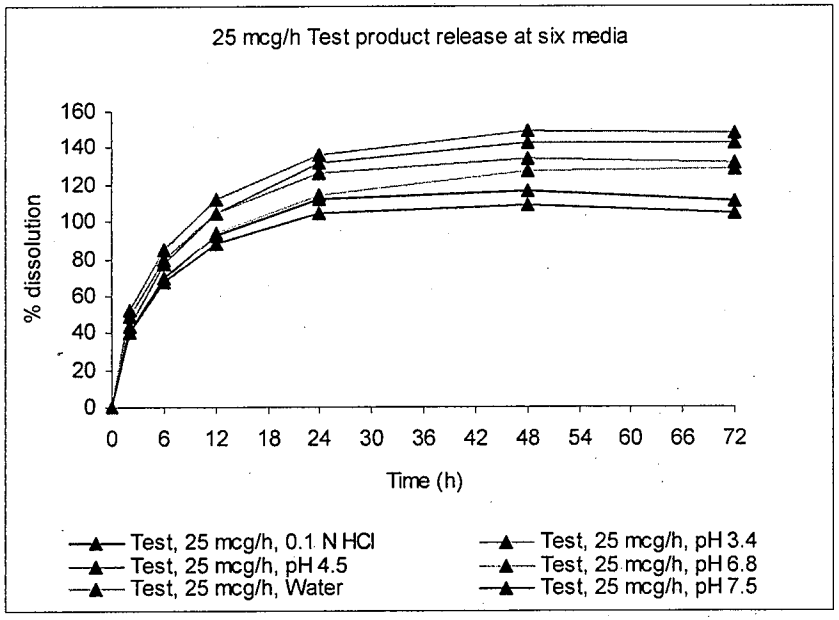
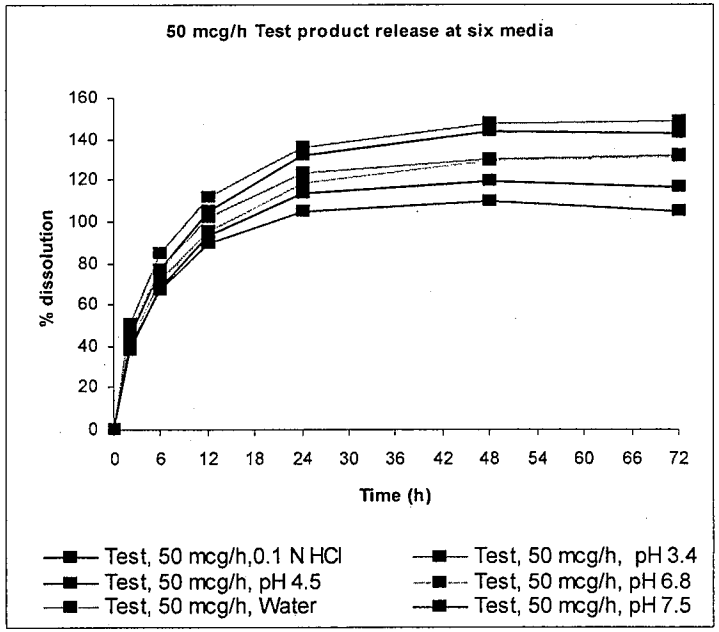
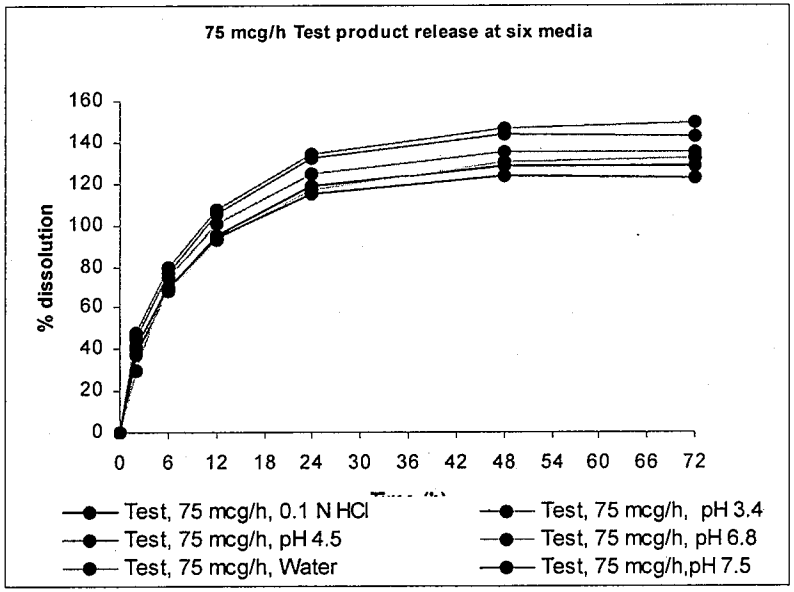
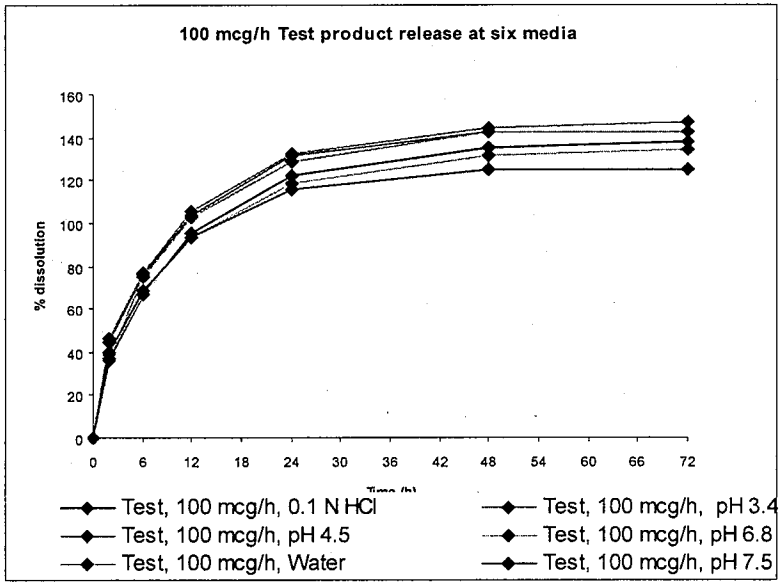


Figure 3 Effect of pH on the dissolution profiles for test products.









D. Consult Reviews

None

E. SAS Output

Active Component	SAS DATA	SAS PROGRAM	SAS OUTPUT
Transdermal system BE study	data.xls	fastprogram.txt	output.txt

F. Additional Attachments (not to be released under FOI)

Table 1 Drug content and drug delivery area for different ANDAs

Dose (µg/h)	Test product (Teva, 77449)		Reference product		Test product (Mylan, 76258)		Test product (b) (4)		Test product (Mylan, 76709)		Test product (b) (4)	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	10.7	2.76 (b) (4)	10	2.5	6.25	2.55	(b) (4)		10	2.5	(b) (4)	
50	21.4	5.52	20	5	12.5	5.1			20	5		
75	32.1	8.28	30	7.5	18.75	7.65			30	7.5		
100	42.8	11.04	40	10	25	10.2			40	10		

Dose (µg/h)	Test product (Teva, 77051)		Test product (Mylan, 77062)		Test product (Noven, 77-154)	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.75	10	2.5	7.8	2.75
50	20	5.5	20	5	15.6	5.5
75	30	8.25	30	7.5	23.4	8.25
100	40	11.0	40	10	31.2	11.0

Table 2 Dissolution History from Previous Applications

Firm	Alza	Mylan	(b) (4)	Watson
	INNOVATOR: NDA 19-813*	ANDA 76-258		ANDA 76-709
Medium	0.026M H3PO4 and 0.05 M Na2HPO4	0.1M Phosphate Buffer pH 3.5		0.05 M Phosphate buffer pH 6.5
Volume (mL)	250 ml (change the medium into fresh medium at the time intervals)	600 ml		200 ml
Apparatus	6 (Cylinder)	5 (paddle over disk)		7
Rotation	0.5 cycle per sec	50 (rpm)		30 dips/min
Specifications	For 25 µg/hr 0-2 hr: (b) (4) µg/h; 2-12 hr: (b) (4) µg/h; 12-24 hr: (b) (4) µg/h	0.5 h: (b) (4) 1 h: 2 h: 8 h:		For 25 µg /hour strength: 2 hrs: (b) (4) 12 hrs: 24 hrs: 48 hrs: 72 hrs: For the 50 µg /hour, 75 µg /hour and 100 µg /hour strengths: 2 hrs: (b) (4) 12 hrs: 24 hrs: 48 hrs: 72 hrs:

* Method was obtained from electronic submission for N19-813/SE2-039, submitted 04/05/04.

Firm	(b) (4)	Lavipharm	Abrika	Tyco Hlthcare
		ANDA 77-051	ANDA 77-062	ANDA 77-154
Medium		Isotonic phosphate buffered saline, pH 6.8	0.01 M phosphate buffer pH 6	Phosphate buffer pH 5.5
Volume (mL)		900 ml	500 ml	900 ml
Apparatus		6 (Cylinder)	5 (Paddle over disk)	5 (Paddle over disk)
Rotation		50 rpm	75 rpm	50 rpm
Specifications		1 hour: (b) (4) 6 hours: 24 hours: (b) (4)	2 hrs: NMT (b) (4) 12 hrs: (b) (4) 24 hrs: 48 hrs: 72 hrs: (b) (4)	4 hours: (b) (4) 7 hours: 23 hours: 47 hours:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit the following in connection with the bioanalytical method validation:

   a. Bench-top stability (short-term stability of fentanyl in matrix at room temperature);

   b. Dilution integrity evaluation;

   c. Standard Operating Procedures (SOPs) that were employed during subject sample analysis including those dealing with sample repeats and analytical procedure;

2. You have only submitted the 90% confidence intervals for Ln AUCt, LnAUCinf and LnCmax in the integrated study report, but didn't provide a comprehensive pharmacokinetic and statistical report for this study. Please provide the following information in a tabulated format: 1) mean, standard deviation, coefficient of variation (%CV) and Test/Reference ratios for all derived pharmacokinetic parameters (AUCt, AUCinf, Cmax, Tmax, T1/2 and Kel) and for plasma concentration at each scheduled sampling time, 2) SAS Analyses of Variance report.

3. Please provide the dissolution methods (apparatus, rotation speed, volume and temperature of the media) that were used in your multimedia dissolution testing. For the dissolution data, please provide raw data for individual dosage units, including range values (low, high), CV percentage, or f2 values. In addition, please provide your proposed dissolution method and specification for quality control and stability testing of your product.

4. Please clarify if your multimedia dissolution data were presented as percentage of total delivered dose (µg/hr*24 hr*3. If so, please resubmit those data presented as percentage of labeled amount per patch.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 77-449

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ANDA DUPLICATE
DIVISION FILE
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DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Xiaojian Jiang X.J. 3/30/06
HFD-655/S.Nerurkar 3/30/06
HFD-650/Dale Conner 4/3/06

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BIOEQUIVALENCY - Deficient Submission Date: 12/17/04

1. FASTING STUDY (STF) Strength: 25 ug/hr
Clinical: **Novum Pharmaceutical Research Services** **Outcome: IC**
Analytical: (b) (4)

2. DISSOLUTION WAIVER (DIW) Strength: 50 ug/hr
Outcome: IC

3. DISSOLUTION WAIVER (DIW) Strength: 75 ug/hr
Outcome: IC

4. DISSOLUTION WAIVER (DIW) Strength: 100 ug/hr
Outcome: IC

Outcome Decisions: **IC**- incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-449
Drug Product Name	Fentanyl Transdermal System
Strength	25 µg/hour, 50 µg/hour, 75 µg/hour, and 100 µg/hour
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454
Point of Contact	Philip Erickson
Phone Number	215-591-3000
Fax Number	215-591-8812
Original Submission Date(s) and previous Amendment	3/21/05
Current Amendment Date(s)	**5/3/06 and 01/16/07**
Reviewer	Xiaojian Jiang, Ph.D.
DSI Inspection	**Clinical inspection is ongoing.** **There is no BE inspection scheduled or necessary (routine or for cause)**
First Generic	**no**
File Location	DFS

I. Executive Summary

The firm has previously submitted a transdermal system bioequivalence (BE) study comparing its test product, Fentanyl Transdermal System, 25 µg/hr to the reference listed drug (RLD), Duragesic® Transdermal System, 25 µg/hr (Alza Corporation), in the original application, dated 03/21/05. However, the study was found incomplete due to deficiencies related to the analytical method validation, pharmacokinetic and statistical data reports, and the dissolution testing. (V:\firmsnz\TEVA\ltrs&rev\77449N1204).

The firm submitted the current amendments in response to the Division of Bioequivalence (DBE) deficiency comments, dated 04/12/06. The firm's responses concerning the BE study and the dissolution testing are adequate and acceptable. The BE study and the dissolution testing are thus acceptable. The DBE accepts the firm's proposed dissolution method (500 ml or 900 ml of phosphate buffer pH 6.8 using USP apparatus 6 at 50 rpm) for the test product. However, the DBE recommended different dissolution specifications. The firm should acknowledge the DBE-recommended specification (2 hours: (b) (4)%, 6 hours: (b) (4)%, 12 hours: (b) (4)%, 24 hours: NLT (b) (4)%). The waivers of *in vivo* bioequivalence requirements for the 50-, 75-, and 100-µg/hr transdermal systems are pending the firm's acceptance of the DBE-recommended dissolution specification and submitting satisfactory response to pharm/tox deficiencies mentioned in formulation section (see page 13) and in the Chemistry review (V:\firmsnz\TEVA\ltrs&rev\77449R2). The ANDA is incomplete. **A clinical (not a BE) DSI Inspection is underway.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information

See the review of the original submission.

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B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	---
Single-dose fed	No	---
Steady-state	No	---
In vitro dissolution	No	---
Waiver requests	No	---
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	2

C. Review of Submission

Deficiency-1:

Please submit the following in connection with the bioanalytical method validation:

a. Bench-top stability (short-term stability of fentanyl in matrix at room temperature);

b. Dilution integrity evaluation;

c. Standard Operating Procedures (SOPs) that were employed during subject sample analysis including those dealing with sample repeats and analytical procedure;

Firm's Response:

a. Fentanyl was shown to be stable in matrix at room temperature for a period of 4 hours in conjunction with the evaluation of freeze/thaw stability during method validation

b. Demonstration of dilution integrity is confined to the actual sample bioanalytical report.

c. The following SOPs were submitted.

SOP No.	Effective Date of SOP	SOP Title
LP-BA-012	04/01/2004	Conduct of an Analytical Study
P624.01	12/12/2002	Determination of Fentanyl, (b) (4) and (b) (4) in Human Plasma by LC/MS/MS

Review's Comment

The firm's response to the deficiency 1 is acceptable. However, in the future, the firm should conduct separate bench-top stability and freeze/thaw stability study, and conduct the dilution integrity study in the pre-study bioanalytical method validation instead of in the actual sample assay.

Deficiency-2:

You have only submitted the 90% confidence intervals for Ln AUCt, LnAUCinf and LnCmax in the integrated study report, but didn't provide a comprehensive pharmacokinetic and statistical report for this study. Please provide the following information in a tabulated format: 1) mean, standard deviation, coefficient of variation (%CV) and Test/Reference ratios for all derived pharmacokinetic parameters (AUCt, AUCinf, Cmax, Tmax, T1/2 and Kel) and for plasma concentration at each scheduled sampling time, 2) SAS Analyses of Variance report.

Firm's Response:

The firm provided the requested information**.** The firm's calculated data agree with reviewer's calculations reported in the original application.

Review's Comment

The firm's response to the deficiency 2 is acceptable.

Deficiency-3:

Please provide the dissolution methods (apparatus, rotation speed, volume and temperature of the media) that were used in your multimedia dissolution testing. For the dissolution data, please provide raw data for individual dosage units, including range values (low, high), CV percentage, or f2 values. In addition, please provide your proposed dissolution method and specification for quality control and stability testing of your product.

Firm's Response:

Source of Method (USP, FDA or Firm)	Firm
Medium	The dissolution testing was conducted in various medium: 0.1 HCl; pH 3.4; pH 4.5; pH 6.8; Water and pH 7.5 using the same method listed below.
Volume (mL)	500 mL (25 and 50 µg/h systems) 900 mL (75 and 100 µg/h systems)
USP Apparatus type	USP Apparatus 6 (cylinders)
Rotation (rpm)	50 rpm
Temperature	32 °C
Firm's proposed method and specification	USP Apparatus 6 (cylinders) rotating at 50 rpm with 500 mL (25 and 50 µg/h systems) or 900 mL (75 and 100 µg/h systems) of pH 6.8 Phosphate Buffer at 32 °C. 6 h: (b) (4) % 24 h: % 48 h: % 72 h: % The specifications are presented as percentage of total delivered dose. The reviewer converted them to percentage of total amount contained in the patch as follows: 6 h: (b) (4) 24 h: % 48 h: % 72 h: %
RLD method and specification	The innovator didn't use standard USP apparatus for the Duragesic® product (RLD). Therefore, the DBE has never recommended the innovator's method to other generic firms. Instead, the DBE has recommended various methods to these firms. Please see Dissolution history attached in the original reviewer for DBE-recommended method and specifications.
F2 metric calculated?	Yes, see below
If no, reason why F2 not calculated	NA
Is method acceptable?	Yes, however, the firm needs to acknowledge DBE-recommended specifications.

F2 metric, higher strengths compared to lower strength													
Higher strength	Lower strength	F2 metric for test						F2 metric for RLD					
		Firm's proposed method (pH 6.8)	Water	0.1 N HCl	pH 3.4	pH 4.5	pH 7.5	Firm's proposed method (pH 6.8)	Water	0.1 N HCl	pH 3.4	pH 4.5	pH 7.5
50 µg/hr	25 µg/hr	97.7	84.8	93.9	83.5	84.6	98.9	76.2	89.5	89.3	84.6	72.4	85.4
75 µg/hr	25 µg/hr	71.2	61.0	77.9	86.3	63.2	59.1	58.3	69.2	59.1	61.6	62.8	66.5
100 µg/hr	25 µg/hr	71.9	51.5	69.8	81.4	64.5	58.1	58.7	71.9	59.1	65.4	58.6	61.1

F2 metric, test compared to reference	
Strength	F2 metric
	Firm's proposed method (pH 6.8) (for other media, the F2 values are similar to that of pH 6.8. They are all below 50)
25 µg/hr	27.19
50 µg/hr	25.05
75 µg/hr	22.96
100 µg/hr	23.69

NOTE:

1. The firm submitted dissolution data presented as both a percentage of total dose released (µg/hr*24 hr*3) and a percentage of labeled amount per patch. The data presented as percentage of labeled amount per patch were reported below for all media. For the 25 µg/hr strength, the total dose released is 1.8 mg (25 µg/hr*24 hr*3 days), whereas the labeled amount for the test patch is 2.76 (b) (4) mg.

2. During the process of this review, the reviewer and PM contacted the firm because there is a discrepancy in the media labeling for the datasets reported the original application and the May, 3 amendment. The firm submitted amendment of 1/16/07 and clarified that the data reported in the original application is incorrect. The firm has also submitted an updated report which correctly identified the dissolution datasets.

The Dissolution data are presented in the following tablets:

Table 1 Comparative Dissolution testing using media----A: water

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	26	3.20	(b) (4)	13	4.51	(b) (4)
6	46	2.72		19	4.96	
12	61	2.30		27	3.78	
24	73	1.68		39	3.65	
48	75	1.45		55	4.25	
72	72	2.01		67	3.14	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	25	2.62	(b) (4)	12	7.26	(b) (4)
6	45	2.28		18	6.00	
12	61	2.06		27	6.03	
24	74	2.53		39	7.03	
48	78	3.61		56	7.10	
72	76	4.19		69	4.39	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	24	2.27	(b) (4)	9	9.38	(b) (4)
6	45	1.68		14	7.42	
12	62	1.50		22	4.02	
24	77	1.99		35	6.23	
48	84	3.44		54	4.61	
72	84	4.26		71	3.07	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	24	2.91	(b) (4)	9	7.21	(b) (4)
6	44	1.34		15	6.38	
12	62	0.93		23	6.72	
24	80	0.85		36	6.32	
48	88	0.74		56	3.42	
72	90	1.36		72	4.29	

Table 2 Comparative Dissolution testing using media----B: 0.1 N HCl

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	34	2.49	(b) (4)	17	2.11	(b) (4)
6	56	2.37		25	1.94	
12	73	1.84		33	1.94	
24	89	1.60		47	2.41	
48	97	1.59		65	2.57	
72	97	1.19		76	3.17	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	33	2.59	(b) (4)	15	7.37	(b) (4)
6	55	1.93		23	5.83	
12	73	2.21		32	4.34	
24	89	1.93		46	3.55	
48	96	2.62		64	4.38	
72	96	3.01		74	4.89	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	31	1.87	(b) (4)	12	4.83	(b) (4)
6	52	1.74		18	4.94	
12	70	1.15		26	4.89	
24	87	1.90		39	4.99	
48	96	1.46		58	4.57	
72	97	1.84		71	3.89	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	30	1.96	(b) (4)	12	6.20	(b) (4)
6	50	1.11		18	5.56	
12	68	1.31		26	4.61	
24	86	1.57		39	4.60	
48	94	1.34		58	5.90	
72	96	1.90		70	6.3	

Table 3 Comparative Dissolution testing using media----C: pH 3.4.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	26	1.98	(b) (4)	16	2.53	(b) (4)
6	44	2.04		25	2.33	
12	61	1.72		34	1.90	
24	75	1.08		47	2.74	
48	83	1.36		66	3.39	
72	83	0.89		78	4.14	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	27	2.61	(b) (4)	14	6.03	(b) (4)
6	47	1.66		23	4.97	
12	62	1.47		32	4.74	
24	77	1.16		47	4.80	
48	85	1.01		65	4.91	
72	85	1.18		76	4.91	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	26	1.25	(b) (4)	11	5.27	(b) (4)
6	45	0.72		18	6.07	
12	61	0.97		27	5.14	
24	77	0.77		41	4.43	
48	85	0.94		61	3.67	
72	86	1.04		75	3.18	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	25	1.17	(b) (4)	13	4.44	(b) (4)
6	44	1.57		20	3.70	
12	61	0.79		28	3.39	
24	77	0.91		42	2.79	
48	85	0.89		61	2.68	
72	87	0.81		74	3.06	

Table 4 Comparative Dissolution testing using media----D: pH 4.5.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	32	2.06	(b) (4)	17	2.25	(b) (4)
6	52	1.46		25	5.23	
12	68	2.06		34	3.64	
24	82	1.85		48	4.29	
48	87	1.94		67	4.27	
72	86	2.70		79	4.06	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	30	2.11	(b) (4)	15	5.21	(b) (4)
6	51	2.43		23	8.26	
12	67	1.92		31	3.83	
24	80	1.90		44	3.85	
48	85	2.45		63	5.20	
72	86	3.03		75	6.28	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	20	46.02	(b) (4)	12	5.43	(b) (4)
6	49	1.69		19	5.29	
12	66	1.57		28	4.48	
24	82	2.02		42	3.28	
48	88	2.06		62	2.70	
72	88	2.12		76	2.76	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	24	17.46	(b) (4)	11	7.38	(b) (4)
6	49	2.33		18	6.94	
12	67	1.20		26	6.87	
24	84	1.20		40	6.81	
48	93	1.72		60	5.60	
72	93	2.25		75	4.91	

Table 5 Comparative Dissolution testing using media----D: pH 6.8 (the firm's proposed method)

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	29	1.15	(b) (4)	16	2.30	(b) (4)
6	50	0.67		24	1.95	
12	69	0.82		33	3.41	
24	86	1.19		46	4.46	
48	93	1.96		65	4.79	
72	93	3.05		75	4.26	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	29	1.15	(b) (4)	14	7.69	(b) (4)
6	50	0.87		21	7.40	
12	69	1.08		30	6.78	
24	86	1.47		43	6.44	
48	94	1.87		61	6.38	
72	94	2.29		72	6.20	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	29	0.64	(b) (4)	11	6.42	(b) (4)
6	50	0.38		18	6.39	
12	69	0.62		26	5.96	
24	86	0.83		39	5.55	
48	94	0.76		58	5.35	
72	94	0.75		71	5.68	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	29	1.17	(b) (4)	12	3.95	(b) (4)
6	49	1.39		18	3.58	
12	68	1.01		26	3.51	
24	85	1.56		39	4.20	
48	93	2.30		58	5.16	
72	93	3.15		72	5.34	

Table 6 Comparative Dissolution testing using media----D: pH 7.5.

Sampling Time (h)	Test Product, Strength: 25 µg/hr Lot No. 33938			Reference Product, Strength: 25 µg/hr Lot No. 0323963		
	Mean	%CV	Range	Mean	%CV	Range
2	26	2.38	(b) (4)	15	2.03	(b) (4)
6	44	1.74		23	2.06	
12	58	1.54		30	14.41	
24	69	1.64		43	3.29	
48	71	1.44		59	3.74	
72	68	1.32		69	3.58	
Sampling Time (h)	**Test Product, Strength: 50 µg/hr Lot No. 33945**			**Reference Product, Strength: 50 µg/hr Lot No. 0331768**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	26	2.62	(b) (4)	13	7.51	(b) (4)
6	44	2.14		20	5.88	
12	58	1.63		29	5.12	
24	69	1.24		42	4.99	
48	72	1.42		59	4.66	
72	69	1.48		69	4.75	
Sampling Time (h)	**Test Product, Strength: 75 µg/hr Lot No. 33946**			**Reference Product, Strength: 75 µg/hr Lot No. 0403133**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	27	1.63	(b) (4)	10	4.65	(b) (4)
6	45	1.29		17	4.25	
12	61	1.19		25	3.20	
24	75	1.25		38	2.47	
48	81	1.93		57	3.58	
72	80	1.93		68	3.90	
Sampling Time (h)	**Test Product, Strength: 100 µg/hr Lot No. 33947**			**Reference Product, Strength: 100 µg/hr Lot No. 0307385**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	26	3.13	(b) (4)	10	7.12	(b) (4)
6	44	2.94		16	5.24	
12	61	2.38		24	6.21	
24	75	2.17		36	5.83	
48	82	2.70		53	6.17	
72	81	2.95		66	5.59	

Review's Comment:

Based on the submitted data and consult with the DBE dissolution focal point, Dr. Seo Paul, the DBE accepts the firm's proposed dissolution method as follows:

Medium	Phosphate buffer pH 6.8
Volume (mL)	500 mL (25 and 50 µg/h systems) 900 mL (75 and 100 µg/h systems)
USP Apparatus type	USP Apparatus 6 (cylinders)
Rotation (rpm)	50 rpm
Temperature	32 °C

However, the DBE recommends the following dissolution specifications:

2 hours: (b) (4)
6 hours:
12 hours
24 hours

Please note that the data are presented as percentage of labeled amounts per patch

The firm's response to the deficiency 3 is acceptable.

Deficiency-4:

*Please clarify if your multimedia dissolution data were presented as percentage of total delivered dose (µg/hr*24 hr*3). If so, please resubmit those data presented as percentage of labeled amount per patch.*

Firm's Response:

The firm clarified that the data submitted in the original application were presented as percentage of total delivered dose. The data presented as the percentage of the labeled claim was presented in Responses to Deficiency-3.

Review's Comment:

The firm's response to the deficiency 4 is acceptable.

D. Formulation

Location in appendix	See review of the original application
Are inactive ingredients within IIG limits?	See comments below
If no, list ingredients outside of limits	
If a tablet, is the product scored?	NA
If yes, which strengths are scored?	NA
Is scoring of RLD the same as test?	NA
Is the formulation acceptable?	Pending satisfactory responses to pharm/tox deficiencies
If not acceptable, why?	NA

Comments on the Formulation:

As stated in the review of the original application, two inactive ingredients, Polyisobutene Adhesive and Polybutene (b) (4) were above the IIG limits and not listed in the IIG, respectively. The pharmacology and toxicology (Pharm/Tox) data submitted by the firm were sent for consultation on 6/22/05. According to CMC review#2 (dated 06/12/06), the Pharm/Tox data were found incomplete. The firm needs to address the following comments:

a. The studies do not assess the safety of the dermal route of administration.
b. The materials tested are not the same as the proposed materials.
c. The studies did not determine the actual dose of the materials the rats consumed.
d. The studies do not appear to have been conducted under Good Laboratory Practice Guidelines.

(Please see CMC review#2 located at V:\firmsnz\TEVA\ltrs&rev\77449R2.doc. However, the reviewer could not find the Pharm/Tox review in V drive, DFS or in Jacket)

H. Waiver Request(s)

Strengths for which waivers are requested	50 µg/hr, 75 µg/hr and 100 µg/hr
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes, The formulations are dose-proportional with respect to the area of the delivery surface and the composition of the adhesive matrix.
Is dissolution acceptable?	Yes
Waivers granted?	No
If not then why?	Pending firm's acknowledgement of DBE-recommended dissolution specifications.

I. Deficiency Comments

1. The firm is requested to acknowledge the DBE-recommended dissolution specifications.

2. The Pharm/Tox data for two inactive ingredients, Polyisobutene Adhesive and Polybutene (b) (4) were found incomplete. The firm needs to address Pharm-Tox deficiencies**.**

J. Recommendations

1. The transdermal system bioequivalence study conducted by Teva on its Fentanyl Transdermal System, 25 µg/hr, lot #77082, comparing it to Alza Corporation's Duragesic® Transdermal System, 25 µg/hr, lot #0323963, has been found acceptable.

2. The dissolution testing is acceptable. The firm's proposed dissolution method is acceptable. However, the firm's proposed dissolution specification is not acceptable. The firm should acknowledge the DBE-recommended dissolution specification.

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/h strengths) and 900 ml (for the 75 and 100 µg/h strengths) of phosphate buffer pH 6.8 at 32°C, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours
   24 hours

   (Please note that the specifications are presented as percentage of labeled amounts per patch)

3. The formulations of the 50-, 75-, and 100-µg/hr strengths are proportionally similar to the 25-µg/hr strength of the test product which underwent in vivo bioequivalence testing. The waiver requests for the 50-, 75-, and 100-µg/hr strengths, however, are not granted pending firm's acceptance of DBE-recommended dissolution specification.

4. The Pharm/Tox data for two inactive ingredients, Polyisobutene Adhesive and Polybutene (b) (4), were found incomplete. The firm needs to address Pharm/Tox deficiencies.

The application is incomplete.

IV. Appendix

C. Dissolution Consult

-----Original Message-----
From: Seo, Paul
Sent: Friday, January 19, 2007 12:41 PM
To: Jiang, Xiaojian
Cc: Seo, Paul
Subject: RE: Consult for Fentanyl TDS, ANDA 77449

Hi Xiaojian,

After looking at the firm's data, I would agree with your proposal of specs as follows:

2 hours: (b) (4)
6 hours:
12 hours:
24 hours: %

This provides the firm a discriminatory method but not too stringent. The firm's choice of apparatus and media (6/cylinders, pH 6.8 buffer) are also acceptable. This is just a recommendation, please consult your TL as well.

Thanks,
Paul

-----Original Message-----
From: Jiang, Xiaojian
Sent: Fri 1/19/2007 10:59 AM
To: Seo, Paul
Subject: Consult for Fentanyl TDS, ANDA 77449

Hi, Paul:
Sorry to bother you again.
This is the one that we had talked about. Now I am sending all the data presented as percentage of total amount contained in the patch. Total amount contained in the test patch of 25 mcg/hr is 2.76(b) (4)mg. The total delivered dose is 1.8 mg (25 mcg/hr*72).

Please see attached amendment review for the data and original review for the dissolution history of previous Generic Fentanyl patches.
In the original review, there are deficiencies for their dissolution data. In the amendment, they provided the correct data.

My proposal: The firm's dissolution method is acceptable. But the firm's specification is not acceptable. I suggested as follows:
2 hours: (b) (4)
6 hours:
12 hours:
24 hours: %
What do you think?
<<77449N1204.doc>> <<77449A0506.doc>>

Please let me know if you need more information. Sorry If I am not clear about the information.

Xiaojian

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. We agree with your proposed dissolution method. However, your proposed dissolution specification is not acceptable. Please provide a statement of your acceptance of the following dissolution method and specification:

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/hr strengths) and 900 ml (for the 75 and 100 µg/hr strengths)of Phosphate buffer pH 6.8 at 32°C±0.5°, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours:
   24 hours: %

   (Please note that the specifications are presented as percentage of **labeled amounts** per patch)

2. Your formulation is not acceptable pending a satisfactory response to the deficiencies from the FDA Pharmacology review regarding the toxicology information provided for the adhesives.

The following comments are for your future applications:

1. Please conduct separate bench-top stability and freeze/thaw stability study, and conduct the dilution integrity study in the pre-study bioanalytical method validation instead of in the actual sample assay.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file for all your future application. For the dissolution data, in addition to the mean dissolution data, please also provide raw data for individual dosage units, range values (low, high) and CV percentage.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 1. Summary of Comparative Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (units)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M %CV M %CV	M %CV Med M %CV Med	M %CV M %CV	M %CV M %CV	M %CV M %CV	M %CV M %CV	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M %CV M %CV	M %CV Med M %CV Med	M %CV M %CV	M %CV M %CV	M %CV M %CV	M %CV M %CV	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means*, Ratios of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				

* **Geometric Means Based on Least Squares Means of Ln-transformed Data**

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	@ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	**Conditions of Dissolution Testing:** Apparatus: Speed of Rotation: rpm Medium: Volume: mL Temperature: C± **Proposed Specification:**	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6A. Demographic Profile of Subjects Completing the Comparative Bioavailability Study (Fasting)

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD		
Range		
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 6B. Demographic Profile of Subjects Completing the Comparative Bioavailability Study (Fed)

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD		
Range		
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8A. Reanalysis of Study Samples (Fasting Study)

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of reanalyzed values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

Table 8B. Reanalysis of Study Samples (Fed Study)

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of reanalyzed values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[2]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

CC: ANDA 77-449

BIOEQUIVALENCY - Incomplete Submission Date: 5/03/06, Submission Date: 1/16/06 WC

1. **Study Amendment** (STA) Strengths: all strengths,
Outcome: IC

2. Study Amendment (STA) Strengths: all strengths
Outcome: WC

Outcome Decisions: Incomplete.

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

/s/

Xiaojian Jiang
2/23/2007 10:53:48 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
2/23/2007 10:58:11 AM
BIOPHARMACEUTICS

Dale Conner
2/23/2007 04:51:59 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-449
Drug Product Name	Fentanyl Transdermal System
Strength	25 µg/hour, 50 µg/hour, 75 µg/hour, and 100 µg/hour
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454
Point of Contact	Philip Erickson
Phone Number	215-591-3000
Fax Number	215-591-8812
Original Submission Date(s) and previous Amendment	3/21/05, 05/3/06 and 01/16/07
Current Amendment Date(s)	**4/3/07**
Reviewer	Xiaojian Jiang, Ph.D.
DSI Inspection	**There is no BE inspection scheduled or necessary.**
First Generic	**no**
File Location	DFS
Outcome	incomplete

I. Executive Summary

The firm has previously submitted a transdermal system bioequivalence (BE) study comparing its test product, Fentanyl Transdermal System, 25 µg/hr to the reference listed drug (RLD), Duragesic® Transdermal System, 25 µg/hr (Alza Corporation), in the original application, dated 03/21/05. The study was found incomplete due to deficiencies related to the analytical method validation, pharmacokinetic and statistical data reports, and the dissolution testing. (V:\firmsnz\TEVA\ltrs&rev\77449N1204). In previous amendment dated 5/3/06 and 1/16/07, the firm submitted satisfactory responses concerning the BE study and the dissolution testing (DFS N077449 N000 AB 03-May-2006). The BE study and the dissolution testing was thus found acceptable. The DBE accepted the firm's proposed dissolution method (500 ml for 25 µg/hour, 50 µg/hour or 900 ml for 75 µg/hour, and 100 µg/hour of phosphate buffer pH 6.8 using USP apparatus 6 at 50 rpm). However, the DBE recommended different dissolution specifications (2 hours: (b) (4)%, 6 hours: (b) (4)%, 12 hours (b) (4)%, 24 hours: NLT (b) (4)%). The firm was asked to acknowledge the DBE-recommended specification.

In the current amendment, the firm accepts the DBE recommended specification for the 2, 6 and 12 hrs but proposes a different specification of NLT (b) (4)% at 72 hours. Even though the DBE recommends dissolution specification on the data from the fresh lot and not from the stored lot, the DBE accepting firm's specification in this case because there is no meaningful in vivo and in vitro correlation for this product and in vitro dissolution/release specifications apply throughout the shelf life of this product. (The firm provides room temperature storage dissolution data from 0 to 24 months to support their proposal).

However, the waivers of *in vivo* bioequivalence requirements for the 50-, 75-, and 100-µg/hr transdermal systems are still pending satisfactory pharm/tox consultation results of the firm's submitted toxicology information for the adhesives.

This ANDA is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information

See the review of the original submission and previous amendment.

[(V:\firmsnz\TEVA\ltrs&rev\77449N1204 and DFS N077449 N000 AB 03-May-06)]

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	---
Single-dose fed	No	---
Steady-state	No	---
In vitro dissolution	No	---
Waiver requests	No	---
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	1

C. Review of Submission

Deficiency-1:

We agree with your proposed dissolution method. However, your proposed dissolution specification is not acceptable. Please provide a statement of your acceptance of the following dissolution method and specification:

The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/hr strengths) and 900 ml (for the 75 and 100 µg/hr strengths) of Phosphate buffer pH 6.8 at

32°C±0.5°, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

2 hours: (b) (4)
6 hours:
12 hours:
24 hours: *%*

(Please note that the specifications are presented as percentage of labeled amounts per patch)

Firm's Response:

1. The firm acknowledges that the DBE accepts their proposed dissolution method. However, the firm disagrees with the DBE recommended dissolution specification and proposes the following new specification:

Time (hrs)	**DBE Recommended Specification (% of labeled amount)**	**Currently Firm Proposed Specification (% of labeled amount)**
2	(b) (4)	(b) (4)
6		
12		
24		---
72	---	NLT (b) (4)

The firm also proposes the following acceptance criteria according to Acceptance Table 1 (see below) which pertains to transdermal delivery systems in USP General Chapter <724> Drug Release, and also incorporates a limit test for the final time point at 72 hrs.

Proposed Acceptance Criteria

Level	L_1			L_2			L_3		
Type	Range			Range			Range		
	Acceptance Criteria			Acceptance Criteria			Acceptance Criteria		
Time Point	Low Range		High Range	Low Range		High Range	Low Range		High Range
2 hr	(b) (4)		(b) (4)	(b) (4)		(b) (4)	(b) (4)		(b) (4)
6 hr									
12 hr									

Level	L_1	L_2	L_3
Type	Limit	Limit	Limit
	Acceptance Criteria	Acceptance Criteria	Acceptance Criteria
Time Point		Average of 12 units is NLT (b) (4)	Average of 24 units is NLT (b) (4)
72 hr	No individual value is LT (b) (4)	No individual value is LT	NMT 2 units of the 24 is L None of the units is LT

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

2. The firm provided mean and individual drug release room temperature stability data from 0 to 24 month to support their proposal (see appendix). The averages and ranges of the mean data from 0 to 24 month and for all strengths and all packaging configurations are presented in the table below:

Time point (hrs)	Average (%)	Min (%)	Max (%)	STD (%)	%CV
2	29	(b) (4)	(b) (4)	1.0	3.6

6	49	(b) (4)	(b) (4)	1.2	2.4
12	66			1.5	2.2
24	82			2.6	3.2
48	91			3.3	3.7
72	91			3.7	4.0

The averages and ranges of the individual release data are summarized by the reviewer as follows:

Time point (hrs)	Average (%)	Min (%)	Max (%)
2	29	(b) (4)	(b) (4)
6	49		
12	66		
24	83		
48	91		
72	92		

Review's Comment

1. The dissolution specifications are generally established on bio-lots and generally not widened based on stability data. However, based on the fact that there is no meaningful in-vivo and in-vitro correlation for this product and in vitro dissolution/release specifications apply throughout the shelf life of the product, the DBE accepts the firm's proposal.

   Furthermore, the total dose delivered **in vivo after 72 hour wear time** for the 2.5 µg/hr strength is 1.8 mg (25 µg/hr*24 hr*3 days), which is 65% of the labeled amount (2.76 (b) (4) mg) for the test patch. **In vitro**, at 12 hrs, 66% of the labeled amount releases from the patch. Therefore, the drug release from the patch is not a rate limiting step for the drug absorption and the release specification beyond 12 hrs is irrelevant to the in vivo performance of the test product.

2. The firm's proposed acceptance criteria are acceptable. However, the firm should include the limit for the average values at 2, 6 and 12 hrs and it should also be corrected that at L3 level not more than 2 units of the 24 units are outside the L2 range and none of the units is outside the L3 range listed above.

The firm's response to the deficiency 1 is acceptable.

Deficiency-2:

Your formulation is not acceptable pending a satisfactory response to the deficiencies from the FDA Pharmacology review regarding the toxicology information provided for the adhesives.

Firm's Response:

The firm acknowledges that a satisfactory assessment of toxicology information for the adhesives is required by the FDA Pharmacology review. Toxicology information pertaining to the adhesives was submitted via the firm's Jan. 3, 2007 minor amendment. In addition, the amendment contained notification of a third party submission from (b) (4) regarding additional toxicology information for the adhesives. The third party submission was resubmitted on March 19, 2007.

Review's Comment

According to the chemistry reviewer, the firm's Toxicology information has been sent for consultation. The consultation review was not yet completed. Therefore, the test formulation is still not acceptable

Please note that by the time of Nov.1, 2007, the consultation review was still not completed.

D. Formulation

Location in appendix	See review of the original application and previous amendment.
Are inactive ingredients within IIG limits?	No for (b) (4) adhesives
If no, list ingredients outside of limits	
If a tablet, is the product scored?	NA
If yes, which strengths are scored?	NA
Is scoring of RLD the same as test?	NA
Is the formulation acceptable?	Pending pharm/tox consultation results.
If not acceptable, why?	NA

H. Waiver Request(s)

Strengths for which waivers are requested	50 µg/hr, 75 µg/hr and 100 µg/hr
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes, The formulations are dose-proportional with respect to the area of the delivery surface and the composition of the adhesive matrix.
Is dissolution acceptable?	Yes
Waivers granted?	No
If not then why?	Pending evaluation of formulation information

I. Deficiency Comments

1. The firm's Toxicology information concerning (b) (4) adhesives has been sent for consultation. The consultation result is pending.

J. Recommendations

1. The transdermal system bioequivalence study conducted by Teva on its Fentanyl Transdermal System, 25 µg/hr, lot #77082, comparing it to Alza Corporation's Duragesic® Transdermal System, 25 µg/hr, lot #0323963, has been found **acceptable**.

2. The dissolution testing is acceptable. The firm's proposed dissolution method and specification are acceptable.

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/h strengths) and 900 ml (for the 75 and 100 µg/h strengths) of phosphate buffer pH 6.8 at 32°C, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours
   72 hours %

   (Please note that the specifications are presented as percentage of labeled amounts per patch)

3. The firm's Toxicology information concerning (b) (4) adhesives has been sent for consultation. The consultation result is pending.

4. The formulations of the 50-, 75-, and 100-µg/hr strengths are proportionally similar to the 25-µg/hr strength of the test product which underwent in vivo bioequivalence testing. The waiver requests for the 50-, 75-, and 100-µg/hr strengths, however, are not granted pending pharm/tox consultation results.

The application is incomplete.

IV. Appendix

F. Dissolution data

Mean data

(b) (4)

TRAY DATA

Strength 2.76 mg / 10.7 cm^2 25 µg/h Batch # 33985

t-o	t-3	t-6	t-9	t-12	t-18	t-24	Mean	Min	Max	STD	%CV
						(b) (4)	28		(b) (4)	0.7	2.49
							48			1.1	2.27
							66			1.3	2.03
							84			1.9	2.27
							92			2.4	2.59
							92			3.0	3.26

Strength 5.5 (b) (4) 21.4 cm^2 50 µg/h Batch # 33988

t-o	t-3	t-6	t-9	t-12	t-18	t-24	Mean	Min	Max	STD	%CV
						(b) (4)	28		(b) (4)	0.6	2.09
							48			0.6	1.21
							66			1.0	1.47
							84			1.3	1.60
							92			2.2	2.43
							92			2.9	3.20

Strength 8.2 (b) (4) 32.1 cm^2 75 µg/h Batch # 33989

t-o	t-3	t-6	t-9	t-12	t-18	t-24	Mean	Min	Max	STD	%CV
						(b) (4)	28		(b) (4)	0.5	1.85
							48			0.8	1.66
							66			0.8	1.20
							84			0.9	1.04
							94			1.0	1.05
							95			1.3	1.34

Strength 11.0 (b) (4) 42.8 cm^2 100 µg/h Batch # 33990

t-o	t-3	t-6	t-9	t-12	t-18	t-24	Mean	Min	Max	STD	%CV
						(b) (4)	27		(b) (4)	0.5	1.85
							47			1.0	2.09
							66			1.4	2.06
							84			2.2	2.65
							93			2.7	2.95
							94			3.5	3.75

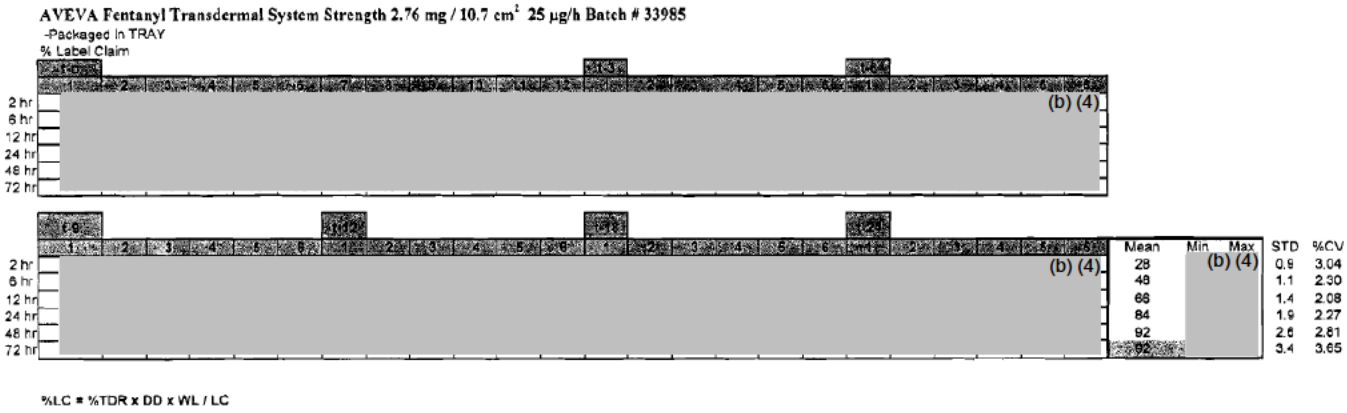
	Mean	Min	Max	STD	%CV
2 hr	28		(b) (4)	0.626	2.25
6 hr	48			0.948	1.98
12 hr	66			1.127	1.71
24 hr	84			1.586	1.89
48 hr	93			2.218	2.39
72 hr	93			2.905	3.11

%LC = %TDR x DD x WL / LC %LC = Percent Label Claim %TDR = Percent Total Dose Release DD = Daily Dose WL = Wear Length

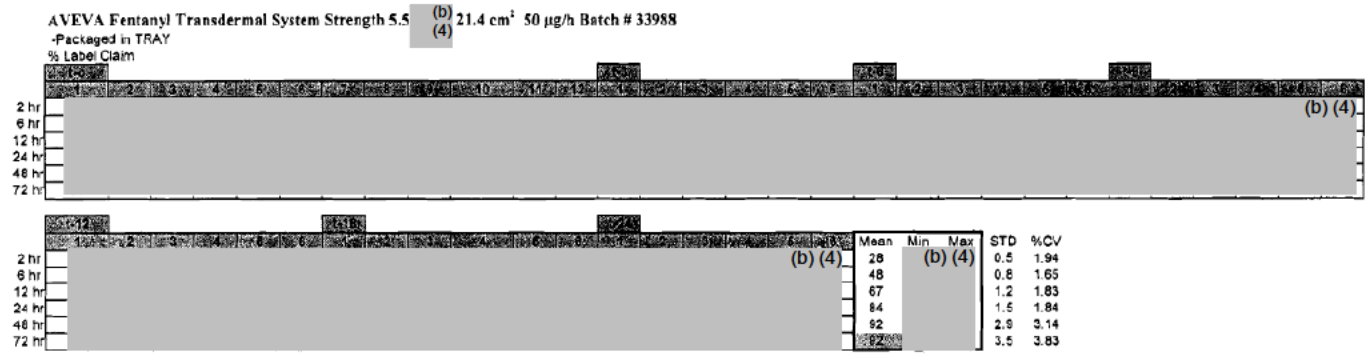
Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

Individual data

(b) (4)



(b) (4)



Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

(b) (4)

AVEVA Fentanyl Transdermal System Strength 8.2 (b) (4) / 32.1 cm² 75 µg/h Batch # 33989
-Packaged in TRAY
% Label Claim

(b) (4)

	Mean	Min	Max	STD	%CV
2 hr	28	(b) (4)		0.6	2.33
6 hr	48			0.8	1.71
12 hr	66			1.0	1.47
24 hr	84			1.0	1.23
48 hr	93			1.4	1.51
72 hr	95			1.8	1.88

(b) (4)

AVEVA Fentanyl Transdermal System Strength 11.0 (b) (4) 42.8 cm² 100 µg/h Batch # 33990
-Packaged in TRAY
% Label Claim

(b) (4)

	Mean	Min	Max	STD	%CV
2 hr	27	(b) (4)		0.6	2.10
6 hr	47			1.0	2.07
12 hr	66			1.4	2.19
24 hr	84			2.3	2.70
48 hr	93			2.8	2.78
72 hr	94			3.5	3.72

C. Dissolution Consult

From: Read, Shanaz
Sent: Thursday, May 10, 2007 4:47 PM
To: Jiang, Xiaojian

Subject: RE: ANDA 77449

Ted Palat, the PM for Team 10 has sent the information for consult to Pharm-Tox. We have not heard back from them yet.

Shanaz

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. We agree with your proposed dissolution method and specification as follows:

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/hr strengths) and 900 ml (for the 75 and 100 µg/hr strengths)of Phosphate buffer pH 6.8 at 32°C±0.5°, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours:
   72 hours: %

   (Please note that the specifications are presented as percentage of **labeled amounts** per patch)

   Your proposed acceptance criteria are acceptable (see below). However, you should include the limit for the average values at 2, 6 and 12 hrs and it should also be corrected that at L3 level, not more than 2 of the 24 units are outside the L2 range and none of the units is outside the L3 range for the 2. 6 and 12 hour time point.

Proposed Acceptance Criteria

Level	L_1		L_2		L_3	
Type	Range		Range		Range	
	Acceptance Criteria		Acceptance Criteria		Acceptance Criteria	
Time Point	Low Range	High Range	Low Range	High Range	Low Range	High Range
2 hr	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
6 hr						
12 hr						

Level	L_1	L_2	L_3
Type	Limit	Limit	Limit
	Acceptance Criteria	Acceptance Criteria	Acceptance Criteria
Time Point		Average of 12 units is NLT (b) (4)	Average of 24 units is NLT (b) (4)
72 hr	No individual value is LT (b) (4)	No individual value is LT	NMT 2 units of the 24 is LT None of the units is LT

2. Your submitted toxicology information pertaining to the adhesives is currently under review. Therefore, the test formulation is still not acceptable pending the FDA Pharmacology/Toxicology review.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77-449

V. *Completed Assignment for 77449 ID: 813*

Reviewer: Jiang, Xiaojian **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
813	4/3/2007	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

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

/s/

Xiaojian Jiang
11/8/2007 08:53:07 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
11/8/2007 08:58:42 AM
BIOPHARMACEUTICS

Barbara Davit
11/9/2007 02:43:08 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77449		
Drug Product Name	Fentanyl Transdermal Patch		
Strength(s)	25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr		
Applicant Name	Teva Pharmaceuticals USA		
Address	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454		
Applicant's Point of Contact	Philip Erickson, R.Ph.		
Contact's Telephone Number	(215) 591-3141		
Contact's Fax Number	(215) 591-8812		
Original Submission Date(s)	December 17, 2007		
Submission Date(s) of Amendment(s) Under Review	Jun 03, 2008 (BE study with and without adhesive overlay)		
Reviewer	Anil K. Nair		
Study Number (s)	10836036		
Study Type (s)	Fasted		
Strength (s)	25 mcg/hour		
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	3320 Walnut Bend Lane Houston, TX 77042-4712		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**COMPLETE**		

1 EXECUTIVE SUMMARY

This application contains the results of fasting bioequivalence (BE) study comparing Teva Pharmaceutical's Fentanyl Transdermal System (patch), 25 mcg/hour, **with** Bioclusive™ overlay to its own Fentanyl Transdermal System (patch), 25 mcg/hour, **without** Bioclusive™ overlay. The study was conducted to demonstrate that the Fentanyl Transdermal System results in equivalent bioavailability of the drug product with or without a Bioclusive™ overlay. The BE study was designed as a single-dose, two-way crossover, four sequence study in healthy male and female subjects. The firm's fasting BE study is acceptable. The results are summarized in the tables below.

Fentanyl Transdermal Patch, Dose 25 mcg/hour
Fasting Bioequivalence Study No. 10836036, N=28 (Male=17 and Female=11)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (pg·hr/mL)	34329.78	30109.44	1.14	108.65	119.65
AUC∞ (pg·hr/mL)	36054.25	31544.03	1.14	108.27	120.66
Cmax (pg/mL)	480.38	426.65	1.13	105.87	119.74

In the original submission, the firm had submitted a bioequivalence study comparing its test product, Fentanyl Transdermal System, 25 mcg/hr to the reference listed drug (RLD), Duragesic® Transdermal System, 25 mcg/hr (Alza Corporation), without any overlay. The firm had also submitted *in vitro* dissolution and formulation data for the test and reference products and these data were subsequently reviewed and found acceptable (see the reviews V:\firmsnz\TEVA\ltrs&rev\77449N1204.doc; DFS N077449 N000AB 03-May-06 and DFS N077449 N000AB 03-April-2007).

The firm performed the statistical analysis as four sequence study and the reviewer analyzed the data as two sequence study and the 90% Confidence Intervals were within the acceptable limits of 80-125%, in both ways. The firm considers it as a four sequence study because treatments were administered according to four sequence (A right arm/B left arm or A left arm/B right arm or B right arm/A left arm of B left arm/A right arm) randomization schedule. The reviewer treated as two sequences, AB and BA, where A is test with an overlay and B is test without an overlay.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is acceptable with no deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Fentanyl Transdermal System, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
Reference Product	Duragesic® Transdermal System, 25 µg/hr (also available as 12.5 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
RLD Manufacturer	Alza Corporation (Jansseen Pharmaceutical Products, LP is the U.S. distributor)
NDA No.	19813
RLD Approval Date	8/07/1990 for 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr 2/04/2005 for the 12.5 µg/hr.
Indication	DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that: • requires continuous, around-the-clock opioid administration for an extended period of time, and • cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

3.2 PK/PD Information

Bioavailability	Following DURAGESIC® application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial DURAGESIC® application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Peak serum concentrations of fentanyl generally occurred between 24 and 72 hours after initial application. Serum fentanyl concentrations achieved are proportional to the DURAGESIC® delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72-hour applications, patients reach and maintain a steady state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.
Food Effect	Not Available
Tmax	38.1 hour following first 72 hour application of Duragesic 25 mcg/h
Metabolism	Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%. Skin does not appear to metabolize fentanyl delivered transdermally.

	This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.
Excretion	Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.
Half-life	Approximately 17 hours (range 13-22 hours)
Drug Specific Issues (if any)	DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl. The safety of DURAGESIC® (fentanyl transdermal system) has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older. DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. **All patients and their caregivers should be advised to avoid exposing the DURAGESIC® application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	25 mcg/hr
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	1. The following studies are recommended to establish bioequivalence of fentanyl transdermal system: a. A single-dose fasting *in-vivo* bioequivalence study comparing Fentanyl Transdermal System, 25 mcg/hr, to the reference listed drug (RLD), Duragesic® (Fentanyl) Transdermal System, 25 mcg/hr. Please administer a naltrexone blockade. b. An *in-vivo* skin irritation/sensitization study using a placebo patch identical to your proposed product without fentanyl. 2. Please measure only the parent compound, fentanyl. 3. Fentanyl Transdermal System, 50 mcg/hr, 75 mcg/hr, and

		100 mcg/hr may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) an acceptable bioequivalence study on the 25 mcg/hr strength, (2) acceptable dissolution testing of the 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr strengths, and (3) proportional similarity in the formulations of the 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr strengths. 4. Please determine the wearability of the test and reference patches by recording adhesion scores. The following is an example of a scoring system for adhesion of a transdermal system (TDS): 0 ≥90% adhered (essentially no lift off of the skin) 1 ≥75% to <90% adhered (some edges only lifting off of skin) 2 ≥50% to <75% adhered (less than half of the system lifting off of skin) 3 ≤ 50% adhered but not detached (more than half of the system lifting off of skin without falling off) 4 patch detached (patch completely off the skin) 5. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using several different media (water, 0.1 N HCl, and pH 4.5, 6.8 and 7.5 buffers). Multipoint dissolution profiles should be obtained using a discriminating agitation speed. A surfactant may be used with appropriate justification. Recommendations for sampling times are provided in USP 27 sections <711> and <724>. The following dissolution method should also be conducted: Apparatus: USP Apparatus 5 Speed: 50 rpm Medium: 0.1M phosphate buffer pH 3.5 Volume: 600 mL Sampling Times: 0.5, 1, 2, and 8 hours or until 80% of the labeled drug content is dissolved. 6. Please develop a validated LC/MS/MS method assay with LOQ < 5 pg/mL. Please refer to the Guidance for Industry: "Bioanalytical Method Validation" for additional information. 7. You may submit complete bioequivalence and skin irritation study protocols for review prior to initiating the studies.
		The Division of Bioequivalence (DBE) has recently provided the following additional recommendations for fentanyl transdermal system: 1. The labeling for the reference listed drug (RLD) fentanyl patches has been amended to include the following statements regarding use of an overlay, "Patients should be advised that if they experience problems with adhesion of the DURAGESIC® patch, they may tape the edges of the patch with first aid tape. If problems with adhesion persist, patients may overlay the

		patch with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™)". 2. As per the Office of Generic Drugs policy, for TDS products, the DBE asks ANDA applicants to conduct a bioequivalence study using an overlay whenever the FDA-approved labeling recommends that an overlay be used with the TDS product. 3. Therefore, an in vivo bioequivalence study comparing the rate and extent of fentanyl absorption from the test Fentanyl Transdermal System, 25 mcg/hr, with and without an overlay is recommended. For the product to be deemed bioequivalent with and without the overlay, the 90% confidence intervals for the geometric mean test (overlay)/reference (no overlay) ratios for AUC and Cmax should fall within the limits of 0.8 to 1.25.

Analytes to measure (in plasma/serum/blood):	Fentanyl
Bioequivalence based on:	(90% CI)
Waiver request of in-vivo testing:	50 µg/hr, 75 µg/hr and 100 µg/hr
Source of most recent recommendations:	Control # 060463
Summary of OGD or DBE History (for details, see Appendix 4.4):	**ANDAs:** 076258 (Mylan); 076709 (Watson); (b) (4) (b) (4); 077051 (Lavipharm); 077154 (Tyco). **Protocols:** 07038 (b) (4); 06046 (Watson) **Controls:** 02711, 02369 (Mylan); 03004, 04663, 03417, 03344, 070565, 04713, 070229 ((b) (4) 03467 (Tyco Health Care); 01550, 02629, 050818 (b) (4); 03226 (Watson); 02280 (b) (4); 02710 (Mallinckrodt); 04153 (Aveva Drug delivery Systems); 051228 ((b) (4) 060463 ((b) (4) **Citizen Petitions:** 041172 (London & Mead); 041044, 041100 (Alza); 041099 (Brook Off)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	N/A	-
Steady-state	N/A	-
In vitro dissolution	N/A	-
Waiver requests	N/A	-
BCS Waivers	N/A	-
Clinical Endpoints	N/A	-
Failed Studies	N/A	-
Amendments	N/A	-

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	(b) (4) Analytical Report, Appendix D, pages 282 through 545 for Protocol No. 10836036
Analyte	Fentanyl
Internal standard (IS)	(b) (4)
Method description	Liquid-liquid extraction
Limit of quantitation (pg/mL)	10.0
Average recovery of drug (%) (Fentanyl)	83.8% [89.7% (15 pg/mL); 81.7% (100 pg/mL); 79.9% (440 pg/mL)]
Average recovery of IS (%) (b) (4)	86.2%
Standard curve concentrations (pg/mL)	10.0, 15.0, 20.0, 50.0, 100, 220, 440, and 500
QC concentrations (pg/mL)	10, 20.0, 32.0, 75.0, 150, 400
QC Intraday precision range (%)	1.20 to 5.74%
QC Intraday accuracy range (%)	-11.1 to 2.10%
QC Interday precision range (%)	2.79 to 4.85%
QC Interday accuracy range (%)	-8.93 to -0.0718%
Bench-top stability (hrs)	28.75 hours at room temperature
Stock stability (days)	1383 days at -20°C
Processed stability (hrs)	55.25 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	509 days at -20°C
Dilution integrity	32.0 pg/mL diluted 2-fold, 1000 pg/mL diluted 6-fold.
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes	
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation:

Acceptable

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)					
					Cmax (units/mL)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T½ (hr)	Kel (hr-1)
Study No. 10836036	Study Title: A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 µg/hr) (Teva) when applied with and without an Adhesive Overlay	Single Application, Randomized, Two-Treatment, Two-Period, Crossover Study	**Test product** Fentanyl Transdermal System, 25 mcg/hr, CII Manufactured by Aveva Drug Delivery Systems, Distributed by Teva Pharmaceuticals USA Lot No. 36623 Exp. Date: 07/2009 BIOCLUSIVE™ Transparent Dressing, 4 in x 5 in Johnson & Johnson MEDICAL Limited Lot No. 0802 Exp. Date: 01/2010 **Ref. product** Fentanyl Transdermal System, 25 mcg/hr, CII Manufactured by Aveva Drug Delivery Systems, Distributed by Teva Pharmaceuticals USA Lot No. 36623 Exp. Date: 07/2009	28 completing (17 M/11 F) Healthy subjects 29.04 ± 7.94 (19 - 44)	496.2143 ± 154.5158 (31.1389) 442.7857 ± 137.4038 (31.0317)	Median 36.0000 (24.0000 – 72.0000) Median 42.0000 (24.0000 – 75.0000)	35362.8199 ± 9306.2248 (26.3164) 31237.0143 ± 8620.2226 (27.5962)	37114.1353 ± 9014.8047 (24.2894) 32789.7886 ± 9176.7039 (27.9865)	33.5989 ± 12.6480 (37.6441) 34.1362 ± 10.3227 (30.2397)	0.0226 ± 0.0064 (28.3838) 0.0222 ± 0.0074 (33.3145)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Fentanyl Transdermal Patch Dose 1 x 25mcg/hour Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. 10836036)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	34329.78	30109.44	1.14	108.65	119.65
AUC∞ (pg·hr/mL)	36054.25	31544.03	1.14	108.27	120.66
Cmax (pg/mL)	480.38	426.65	1.13	105.87	119.74

Table 3. Reanalysis of Study Samples

Study No. 10836036								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical - Result above the upper limit of Quantitation	5.0	4.0	0.89%	0.72%	5.0	4.0	0.89%	0.72%
-Result below raised lower limit of quantitation.	1.0	2.0	0.18%	0.36%	1.0	2.0	0.18	0.36
Total	6.0	6.0	1.07%	1.07%	6.0	6.0	1.07%	1.07%

Did use of recalculated plasma concentration data change study outcome?

No

Comments from the Reviewer:

A total of 12 samples (six each from test and reference) were reanalyzed since these samples were outside the limit of quantitation.

3.7 Formulation

Location in appendix	Reviewed Earlier (V:\firmsnz\TEVA\ltrs&rev\77449N1204.doc)
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Reviewed Earlier (N 077449 N 000 AB 03-Apr-2007)
Source of Method (USP, FDA or Firm)	
Medium	
Volume (mL)	
USP Apparatus type	
Rotation (rpm)	
DBE-recommended specifications	
If a modified-release tablet, was testing done on ½ tablets?	
F2 metric calculated?	
If no, reason why F2 not calculated	
Is method acceptable?	
If not then why?	

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	N/A

3.10 Deficiency Comments

None

3.11 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study # 10836036 conducted by the Teva Pharmaceuticals on its Fentanyl Transdermal Patch 25 mcg/hour (lot # 36623), **with** Bioclusive™ overlay **(**lot **#** 0802**)**, comparing it to Teva's own Fentanyl Transdermal Patch, 25 mcg/hour (lot # 36623), **without** Bioclusive™ overlay.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	10836036
Study Title	A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 µg/hr) (Teva) when applied with and without an Adhesive Overlay
Clinical Site	Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, TX 77042-4712
Principal Investigator	Soran Hong, M.D.
Dosing Dates	Period I: April 19, 2008 Period II: May 03, 2008
Analytical Site	(b) (4)
Analysis Dates	Analysis began on May 14, 2008 and was completed on May 20, 2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	31 days 1st collection date – April 19, 2008 Last analysis date – May 20, 2008 First analysis date- May 14, 2008

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Fentanyl Transdermal System, 25 µg/hr with Bioclusive™ Transparent Dressing	Fentanyl Transdermal System, 25 µg/hr
Manufacturer of Drug Product	AVEVA Drug Delivery Systems, Distributed by Teva	AVEVA Drug Delivery Systems, Distributed by Teva
Manufacturer of Bioclusive™ Overlay	Johnson & Johnson MEDICAL Limited	N/A
Batch/Lot No. of Drug Product	36623	36623
Batch/Lot No. of Bioclusive™ Overlay	0802	N/A
Manufacture Date of Drug Product	7/17/07	7/17/07
Expiration Date of Drug Product	07/09	07/09
Expiration Date of Bioclusive™	01/2010	N/A

Overlay		
Strength	25 µg/hr	25 µg/hr
Dosage Form	Film, Extended Release	Film, Extended Release
Production Batch Size	(b) (4) units	(b) (4) units
Potency	97.8% LC 2.70 mg/unit	97.8% LC 2.70 mg/unit
Content Uniformity	Mean: 97.6% LC (2.69 mg/unit) Range: 96.1 – 98.8% LC %RSD: 0.8	Mean: 97.6% LC (2.69 mg/unit) Range: 96.1 – 98.8% LC %RSD: 0.8
Dose Administered	1 patch for 72 hours in each period of the study	1 patch for 72 hours in each period of the study
Route of Administration	Transdermal	Transdermal

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	30 subjects dosed in period I and 28 subjects in period II and all 28 subjects completed the study
No. of Sequences	4; Sequence 1: RtA LtB 2: LtA, RtB 3: RtB, LtA 4: LtB, RtA A (Fentanyl patch with overlay); B (Fentanyl patch without overlay); Rt= Right arm; Lt= Left arm
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	RtA, LtB: 1, 8, 11, 16, 18, 23, 26, 29 LtA, RtB: 2, 6, 10, 14, 19, 24, 28 RtB, LtA: 4, 7, 9, 13, 20, 22, 27, 30 LtB, RtA: 3, 5, 12, 15, 17, 21, 25
Blood Sampling Times	Pre-dose, 3, 6, 12, 24, 36, 42, 48, 60, 72 (prior to removal), 75, 78, 82, 88, 96, 108, 120, 132, 144, 168 hours
Blood Volume Collected/Sample	6 mL/sample (20 collections per period)
Blood Sample Processing/Storage	K_2EDTA tubes were used for sample collection. Samples were centrifuged at 3000 rpm for 120 min at 4oC and the plasma was separated and stored at -20°C (±5°C) until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours prior to dosing and 4 hours after the patch application
Length of Confinement	12 hours prior to dosing until after the 144 hour blood collection
Safety Monitoring	Throughout the study period

Comments on Study Design:

The study design is acceptable. Approximately 12 and 1 hours (±30 minutes) prior to fentanyl patch application and approximately every 12 hours (±30 minutes) after patch application all subjects were given a 50 mg oral naltrexone tablet with 240 ml of water. The final dose of naltrexone was given at 96 hours (approximately 24 hours after the patch was removed). A mouth check was performed to ensure that the tablets were swallowed. If subjects developed opioid-related adverse events during the study, then the investigators, at their discretion, could give additional naltrexone as appropriate, with careful recording of the time and dose.

A single fentanyl transdermal patch delivery system (25 mcg/h) was applied for 72 h in each period. Subjects received the transdermal system with the overlay applied in one of the study periods and the transdermal system without the overlay applied in other study period. Johnson and Johnson BIOCLUSIVE® transparent dressing sterile 4x5 inch product #JNJ2463 (lot #0802, expiry date: 01/2010) was used. Treatments were administered according to two-treatment, four sequence (A right arm/B left arm or A left arm/B right arm or B right arm/A left arm of B left arm/A right arm) randomization schedule.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

SUBJECTS COMPLETING THE STUDY (N = 28)	
Gender	
Males	17 (60.71%)
Females	11 (39.29%)
Race	
American Indian	0 (0.00%)
Asian	0 (0.00%)
Black	23 (82.14%)
Pacific Islander	0 (0.00%)
White	4 (14.29%)
Other	1 (3.57%)
Ethnicity	
Hispanic/Latino	4 (14.29%)
Not Hispanic/Latino	24 (85.71%)
Age (years)	
Mean ± SD	29.04 ± 7.94
Median	27.00
Minimum	19
Maximum	44
Age Groups	

< 18	0 (0.00%)
18 – 40	25 (89.29%)
41 – 64	3 (10.71%)
65 – 75	0 (0.00%)
> 75	0 (0.00%)
Weight (lbs)	
Mean ± SD	74.72 ± 9.70
Median	73.80
Minimum	54.9
Maximum	89.1
BMI (Kg/m^2)	
Mean ± SD	24.57 ± 2.97
Median	25.30
Minimum	19.0
Maximum	29.6
Tobacco User	
Yes	0 (0.00%)
No	28 (100.00%)

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 10836036				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
13	Voluntary withdrew	I	No	N/A
20	Dropped from study	I	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Bioequivalence Study Study No. 10836036	
	Test A N (%)	Reference B N (%)
General Disorders and Administration Site Conditions		
Asthenia	1 (3.57%)	0 (0.00%)
Gastrointestinal Disorders		
Abdominal pain upper	2 (7.14%)	1 (3.33%)
Abdominal pain lower	1 (3.57%)	0 (0.00%)
Constipation	1 (3.57%)	0 (0.00%)
Nausea	3 (10.71%)	6 (20.00%)
Stomach discomfort	1 (3.57%)	1 (3.33%)
Vomiting	1 (3.57%)	4 (13.33%)
Investigations		
Body temperature increased	0 (0.00%)	1 (3.33%)
Blood pressure increased	0 (0.00%)	2 (6.67%)
Blood pressure decreased	0 (0.00%)	1 (3.33%)
Metabolism and Nutrition Disorders		
Anorexia	0 (0.00%)	1 (3.33%)
Musculoskeletal and Connective Tissue Disorders		
Limb discomfort	1 (3.57%)	1 (3.33%)
Nervous System Disorders		
Headache	4 (14.29%)	3 (10.00%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	0 (0.00%)	1 (3.33%)
Pharyngolaryngeal pain	0 (0.00%)	1 (3.33%)
Vascular Disorder		
Dizziness	2 (7.14%)	2 (6.67%)
TOTAL	7 (25.00%)	10 (33.33%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No.		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
The protocol states that the blood pressure, pulse rate, and respiratory rate (sitting) will be measured at approximately (± 30 minutes) 12 hours after the patch has been applied. For subject 02, and subjects 04 through 30, the vital signs were performed from -1 to -15 minutes out of the allowable ± 30 minute window during Period I due to staff error. The Investigators determined that these minimal deviations of vital sign recording times did not affect the subjects' safety and did not compromise the integrity of the data.	02, 06, 08, 10, 11, 14, 16, 18, 19, 23, 24, 26, 28, 29	04, 05, 07, 09, 12, 13, 15, 17, 20, 21, 22, 25, 27, 30

The protocol states that naltrexone will be administered approximately one hour (± 30 minutes) prior to the fentanyl patch application. Subject 03 (b) (6) was administered with naltrexone in Period I eight (8) minutes outside of the ± 30 minute window due to subject replacement after pre-dose blood draw. The Investigators determined that the minor time deviation in the dosing of naltrexone in the alternate that substituted did not affect subject safety or the integrity of the study data.		03

Comments on Dropouts/Adverse Events/Protocol Deviations:

The study started with 30 subjects and 28 subjects completed the study.
Two subjects were withdrawn from the study.
Subject #13 voluntarily withdrew during Period II check-in and was dropped from the study.
Subject #20 did not return for Period II check-in and was dropped from the study.

A total of 42 adverse events (17 Test, 25 Reference) were reported by 17 subjects.
These adverse events were mild in severity.
The adverse events and protocol deviations did not compromise the integrity of the study.

Adhesion Study:

The adhesive properties of the patches were assessed immediately after patch application and at 3, 6, 12, 24, 36, 48, 60 and 72 h.

All patch systems were observed immediately after application and at 3, 6, 12, 24, 36, 48, 60, and 72 hours after application for assessment of adhesion. Due to operational time constraints, the allowable time deviation for patch adhesiveness assessment was ± 10 minutes. The following rating scale was used to assess adhesion:

ADHESION SCORING

Score Adhesion

0 = ≥ 90% adhered (essentially no lift off of the skin)
1 = 75% to <90% adhered (some edges only lifting off of the skin)
2 = 50% to <75% adhered (less than half of the system lifting off the skin)
3 = < 50% adhered but not detached (more than half the system lifting off of the skin but not detached)
4 = Patch detached (patch completely off the skin)

Adhesion results were tabulated but not subjected to formal statistical analysis. None of the patches completely detached during the 72 hour period. The mean adhesion score at each time point by treatment is tabulated below:

Adhesion Score Time Point (Hours)	**Test Patch A (with overlay)**	**Reference Patch B (without overlay)**
	Mean Average	Mean Average
0	0.00	0.00
3	0.00	0.00
6	0.00	0.00
12	0.00	0.00
24	0.00	0.04
36	0.00	0.21
48	0.00	0.25
60	0.00	0.14
72	0.11	0.21

The test patch (with overlay) and reference patch (without overlay) showed comparable adhesion during the 72 hour period.

The subject #2 in period 2 showed adhesion score of 3 (more than half of the system lifting off the skin but not detached) from 36 hour onwards.

FENTANYL
STUDY NO. 10836036

Patch Adhesiveness

Part. No.	Initials	Period	Treatment*	0 Hr**	3 Hr**	6 Hr**	12 Hr**	24 Hr**	36 Hr**	48 Hr**	60 Hr**	72 Hr**
1	(b) (6)	1	A	(b) (4)								
1		2	B									
2		1	A									
2		2	B									
3		1	B									
3		2	A									
4		1	B									
4		2	A									
5		1	B									
5		2	A									
6		1	A									
6		2	B									
7		1	B									
7		2	A									
8		1	A									
8		2	B									
9		1	B									
9		2	A									
10		1	A									
10		2	B									
11		1	A									
11		2	B									
12		1	B									
12		2	A									
13		1	B									
13		2	DFS									
14		1	A									
14		2	B									
15		1	B									
15		2	A									
16		1	A									
16		2	B									
17		1	B									
17		2	A									
18		1	A									
18		2	B									
19		1	A									
19		2	B									
20		1	B									
20		2	DFS									
21		1	B									
21		2	A									
22		1	B									
22		2	A									
23		1	A									
23		2	B									
24		1	A									
24		2	B									
25		1	B									
25		2	A									
26		1	A									
26		2	B									
27		1	B									
27		2	A									
28		1	A									
28		2	B									
29		1	A									
29		2	B									
30		1	B									
30		2	A									

* Study Drug Last Administered: A-Test; B-Reference
** Adhesion Scoring
0 ≥ 90% adhered (essentially no lift off of the skin)
1 = 75% to < 90% adhered (some edges only lifting off of the skin)
2 = 50% to < 75% adhered (less than half of the system lifting off the skin)
3 = < 50% adhered but not detached (more than half the system lifting off of the skin but not detached)
4 = patch detached (patch completely off the skin)
DFS=Did Not Finish the Study

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 10836036 Analyte Name: Fentanyl								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	10.0	15.0	20.0	50.0	100	220	440	500
Inter day Precision (%CV)	5.12	3.13	3.21	3.71	2.69	3.28	2.35	3.44
Inter day Accuracy (%Actual)	100	99.8	99.3	101	101	100	99.0	99.6
Linearity	(Range of R^2 values) 0.9983 to 0.9995							
Linearity Range (pg/mL)	10.0 to 500							
Sensitivity/LOQ (pg/mL)	10.0							

Bioequivalence Study No. 10836036 Analyte Name: Fentanyl					
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	20.0	32.0	75.0	150	400
Inter day Precision (%CV)	5.22	6.27	4.55	3.90	3.05
Inter day Accuracy (%Actual)	88.9	88.8	93.9	92.5	93.4

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms:

Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LP-BA-002	15-Jan-2006	Guidelines for Excluding Data from Bioanalytical Assays
LP-BA-012	01-Sept-2006	Conduct of an Analytical Study

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

None

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. 10836036									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *pg/ml)	35362.82	26.32	20281.70	55787.85	31237.01	27.60	17305.81	51799.80	1.13
AUC∞ (hr *pg/ml)	37114.14	24.29	23385.57	59476.82	32789.79	27.99	18726.54	54012.19	1.13
Cmax (pg/ml)	496.214	31.14	259.00	832.00	442.786	31.03	205.00	748.00	1.12
Tmax* (hr)	36.000	.	24.00	72.00	42.000	.	24.00	75.00	0.86
Kel (hr^{-1})	0.023	27.03	0.01	0.04	0.023	38.02	0.01	0.05	1.03
T1/2 (hr)	33.599	37.64	17.12	84.63	34.136	30.24	14.73	63.75	0.98

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Fentanyl Transdermal Patch 25 mcg/hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 10836036				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	34264.02	30051.76	1.1402	1.0891 – 1.1936
AUC∞ (hr *ng/ml)	35968.02	31468.59	1.1430	1.0831 – 1.2062
Cmax (ng/ml)	473.66	420.68	1.1259	1.0620 – 1.1937

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Fentanyl Transdermal Patch Dose: 25 mcg/h Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No.					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	34329.78	30109.44	1.14	108.65	119.65
AUC∞ (hr *ng/ml)	36054.25	31544.03	1.14	108.27	120.66
Cmax (ng/ml)	480.38	426.65	1.13	105.87	119.74

Table 17. Additional Study Information, Fasting Study No. 10836036

Root mean square error, AUC0-t	0.1002	
Root mean square error, AUC∞	0.1102	
Root mean square error, Cmax	0.1279	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	25	27
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	28 (<10 pg/mL)	28 (<10 pg/mL)
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	25	0.95	0.70	0.99
Reference	27	0.95	0.80	0.99

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm calculated pharmacokinetic parameters and 90% confidence intervals for Fentanyl based on four sequence study.
2. The reviewer calculated pharmacokinetic parameters and 90% confidence intervals for Fentanyl based on two sequence study.
3. The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC\infty$ and $\ln C_{max}$ for Fentanyl are within the acceptable limits of 80-125% in both ways.

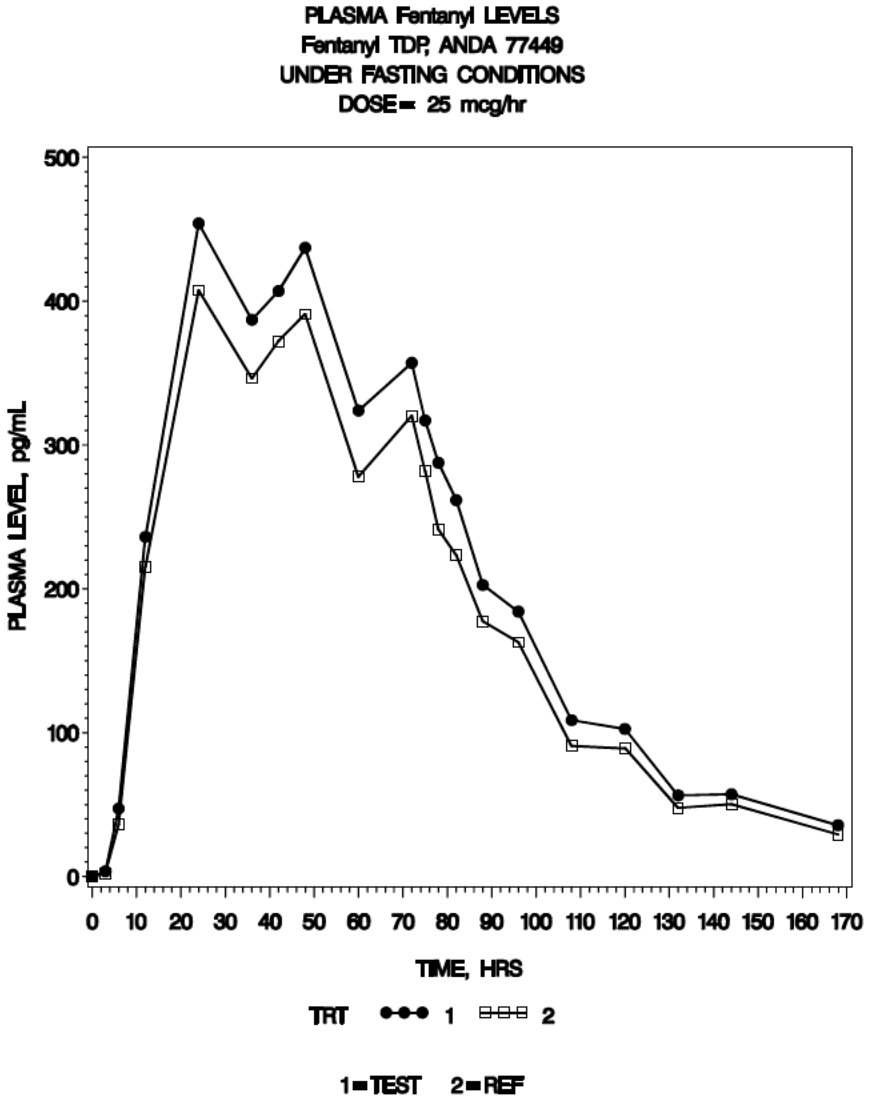
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting in vivo bioequivalence study is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Fentanyl					
Time (hr)	Test (n= 28)		Reference (n= 28)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
3.00	3.56	407.69	2.19	419.22	1.62
6.00	47.26	162.31	36.31	135.79	1.30
12.00	236.17	67.24	215.58	61.77	1.10
24.00	454.18	37.85	407.54	33.27	1.11
36.00	387.11	36.89	346.36	37.30	1.12
42.00	407.07	28.92	372.29	36.57	1.09
48.00	437.21	25.71	391.00	29.30	1.12
60.00	324.00	26.61	277.89	28.79	1.17
72.00	357.14	29.39	320.36	26.69	1.11
75.00	317.14	28.93	281.86	25.46	1.13
78.00	287.75	31.87	241.46	26.70	1.19
82.00	261.71	30.75	223.43	30.96	1.17
88.00	202.66	30.48	177.43	28.00	1.14
96.00	184.21	33.82	162.89	29.79	1.13
108.00	108.65	39.69	90.76	37.24	1.20
120.00	102.57	42.27	89.19	45.32	1.15
132.00	56.39	48.37	47.63	48.10	1.18
144.00	57.17	47.28	50.27	47.18	1.14
168.00	35.66	72.79	29.23	62.12	1.22

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data

Reviewed Earlier (V:\firmsnz\TEVA\ltrs&rev\77449N1204.doc)

4.3 Dissolution Data

Dissolution Review Path	Reviewed Earlier (N 077449 N 000 AB 03-Apr-2007)

Table 19. Dissolution Data

Reviewed Earlier

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

4.6 SAS Output

4.6.1 Fasting Study Data

FASTING CONCENTRATION DATASET

Following this page, 35 pages withheld in full - (b)(4) SAS Data

4.7 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77449

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal Patch
25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time.

We agree with the use of the following dissolution method and specifications:

Method: 500 mL (for the 25 and 50 mcg/hour strengths)and 900 mL (for the 75 and 100 mcg/hour strengths)of phosphate buffer, pH 6.8 at temperature 32°C ± 0.5°C using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specifications
Specifications:

2 hr: (b) (6)
6 hr:
12 hr:
72 hr: %

(Please note that the specifications are presented as percentage of labeled amounts per patch)

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 77449

Completed Assignment for 77449 ID: 6029

Reviewer: Nair, Anil **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Bioequivalence Review (amendment)

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***		
6029	6/3/2008	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
				Bean Total:	1		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

BE Study Fasting	
Clinical	1
Bioanalytical	1
Statistical Analysis	1
Fasting Study Total	*3*

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

/s/

Anil K Nair
8/4/2008 08:20:45 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
8/4/2008 08:52:54 AM
BIOPHARMACEUTICS

Moheb H. Makary
8/9/2008 11:22:36 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

Review of Skin Irritation, Sensitization, And Adhesion Studies

ANDA # 77-449 Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr Teva Pharmaceuticals USA

Sarah H. Seung, Pharm.D.
Clinical Reviewer
Office of Generic Drugs
Date of Review: September 19, 2008

Dates of submissions reviewed:
December 17, 2004
April 20, 2005
June 15, 2005
January 31, 2007 (Datasets)
August 30, 2007

Table of Contents

Clinical Review for ANDA 77-449

Executive Summary

I. Recommendation on Approval

The data submitted to ANDA 77-449 are sufficient to demonstrate that the **skin irritation potential** of the Teva Pharmaceuticals USA (Teva) placebo fentanyl transdermal system (TDS) is no worse than that of the positive controls (0.02% and 0.04%sodium lauryl sulfate) of low irritancy. The data also demonstrate minimal potential of the placebo fentanyl TDS to induce **sensitization**, as expected with use of the RLD, Duragesic®. The data also demonstrate that the **adhesive performance** of the Teva's fentanyl TDS is at least as good as that of the RLD. Therefore, the Clinical Review Team recommends that this application be approved.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Fentanyl Transdermal System (TDS), 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr is a prescription synthetic opioid analgesic indicated for the management of persistent, moderate to severe chronic pain that require continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids. Teva conducted two skin irritation and sensitization studies, 37 healthy subjects in one study and 220 healthy subjects in the second study, to establish the irritation, adhesion and sensitization potential of their proposed Fentanyl Transdermal System. Teva also conducted a pharmacokinetic study, enrolling 36 healthy subjects, during which the adhesion performance of their proposed TDS was also evaluated. In the two skin irritation and sensitization studies each subject received all of the following test articles: a placebo version of Teva's proposed TDS 25 mcg/hr, positive controls (0.02% sodium lauryl sulfate (SLS) and 0.04% SLS) and a negative control (0.9% sodium chloride). The test articles were randomized to different skin application sites on each subject. During the pharmacokinetic study, all subjects received Teva's proposed fentanyl TDS 25 mcg/hr and the reference listed drug (RLD), Duragesic® (Alza Corporation), in a randomized crossover study design.

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of the generic product are no greater than those of the RLD and that the generic product adheres to the skin as well as the RLD over the intended duration of wear.

B. Comparative Irritation

In the 37-subject irritation study (770-0407-01), the data from the daily placebo TDS was compared to that of the daily negative control (0.9% sodium chloride) and the daily positive controls (0.02% and 0.04% Sodium Lauryl Sulfate (SLS)). The FDA statistical review confirmed that the study data showed the irritation potential of the placebo TDS to be worse than the negative control but no worse than that of the positive controls. The non-inferiority test was passed for the daily placebo TDS versus both positive controls, therefore meeting the established criteria to support approval of the application.

C. Comparative Sensitization

Using the definition of a numeric dermal response score of ≥ 1 AND a letter response, none of the subjects in the sensitization study (770-0407-03) was considered potentially sensitized 48 hours and 72 hours following removal of the challenge patch. Therefore, the potential of the placebo fentanyl TDS to induce sensitization would be minimal, as is expected with use of the RLD.

D. Comparative Adhesion

In the 36 subject pharmacokinetic study (770-0407-02), Teva's proposed Fentanyl TDS was compared to the RLD. The FDA statistical consultant confirmed that the mean adhesion scores from the pharmacokinetic study demonstrate non-inferiority of the proposed Fentanyl TDS compared to the RLD.

Clinical Review

I. Introduction and Background

Fentanyl TDS provides continuous systemic delivery of fentanyl, a potent synthetic opioid analgesic specific for the opioid μ-receptor, for 72 hours. It is indicated for the management of chronic pain that cannot be managed by lesser means in opioid tolerant patients.

The reference product, Duragesic®, was approved without skin irritation and contact sensitization studies because of safety concerns with administering narcotics in normal volunteers. (At the time that Duragesic® was approved, Naltrexone was not yet available, so there was no way to block the opioid effects for normal volunteers).

At the time that the studies for this ANDA were designed and conducted, a *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* was posted on the FDA website Guidance Page to assist generic sponsors in designing such studies. That Guidance has subsequently been withdrawn because it was found to be inadequate to address the differences between products with regard to safety considerations, intended duration of wear, and recommended conditions of use. It was also inadequate with regard to recommendations for study analysis and parameters for success.

The sample size recommended in the Guidance for irritation evaluation was only 30 subjects, the same number of subjects commonly enrolled into studies designed to characterize the

irritation potential of new dermatologic products. For the sensitization study, 200 subjects were recommended, the same number of subjects commonly studied to characterize the sensitization potential of new dermatologic products.

The guidance recommended using the highest approved strength of the product and applying both test and reference patches to the same subjects daily to the same skin site for 21 days for induction of maximum irritation potential. For evaluation of sensitization, the guidance recommended same site applications of both test and reference products to the same subjects 3 times per week for 21 consecutive days followed by a 2-week rest period and then a 48-hour challenge application to a naïve site. The application sites were to be observed daily for 3 days after removal of the challenge application for evaluation of potential sensitization. Although the Guidance stated that the studies for sensitization and irritation could be combined into a single study, using 3 times weekly patch applications, that approach was not strongly encouraged.

As numerous sponsors were designing and conducting these studies to evaluate generic fentanyl transdermal systems, the Office of Generic Drugs (OGD) received data showing transient alarmingly high serum fentanyl concentrations in some healthy subjects receiving 25 mcg/hr fentanyl TDS in a pilot skin irritation and sensitization study. This data prompted OGD, in consultation with the Division of Critical Care, Anesthesia, and Addiction Drug Products and the Division of Dermatologic and Dental Drug Products in 2002, to recommend that such studies be conducted with a placebo of the intended patch that is identical to the proposed product in all respects except for the absence of fentanyl. A positive control of low irritancy (0.1% sodium lauryl sulfate (SLS) and a negative control (0.9% saline) were recommended as comparators, with the requirement that the generic product will not be approved unless the study shows that the irritation potential of the placebo patch is no greater than that of the positive control. OGD recommended that the evaluation of irritation and sensitization be combined into a single study with patch applications of the intended duration of wear.

Such studies conducted with the placebo patches will not provide a direct comparison to the actual reference product and will not rule out the possibility that an increase in irritation may occur when the drug substance is added. However, some adhesive components may produce skin irritation, and given that the frequency and degree of skin reactions reported with the Duragesic® patches is relatively low, it is likely that these reactions are produced largely by the adhesive component.

There is currently no *in vitro* method to predict *in vivo* adhesion performance of a transdermal product, and adhesive performance of a placebo patch could change with the addition of the active drug. There are concerns about inadequate adhesion of fentanyl transdermal systems, and it is possible that early patch replacement may contribute to higher serum fentanyl levels that could cause adverse events. Therefore, OGD concluded that adhesive performance of a generic transdermal product must be evaluated by direct comparison of the active generic product vs. the RLD. The pharmacokinetic bioequivalence studies may provide adequate adhesion data if they enroll an adequate number of subjects, collect appropriate adhesion data and do not allow reinforcement of patches.

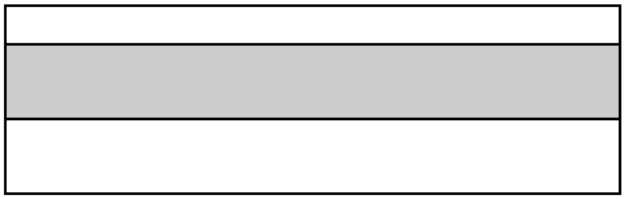
A. Generic Drug Product

1. Drug Established Name: Fentanyl Transdermal System

2. Drug Class: Narcotic Analgesics

3. Product Design of the Fentanyl Transdermal System: The generic TDS has been designed to mimic the performance of Duragesic® transdermal system as closely as possible. The proposed fentanyl transdermal system is a rectangular unit with round corners consisting of an opaque tan backing imprinted with approved artwork, laminated to an overlapping clear release liner. The fentanyl transdermal system is a rectangular unit comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

   a. a backing layer of polyester film;
   b. a fentanyl in polyisobutene adhesive matrix that controls the rate of fentanyl delivery to the skin surface; and
   c. a protective polyester release liner



IMPERMEABLE BACKING

FENTANYL IN POLYISOBUTENE ADHESIVE MATRIX

RELEASE LINER

4. All patches will be manufactured, packaged and tested by Aveva Drug Delivery Systems, Inc., Miramar, Florida in accordance with current Good Manufacturing Practice (GMP).

B. Reference Listed Drug (RLD)

1. RLD Name: Duragesic®

2. NDA number: 19-813

3. NDA Firm: Alza Corporation

4. Date of approval: April 7, 1990

5. Approved Indication(s): management of <u>persistent</u>, moderate to severe chronic pain that:
   - require continuous, around-the-clock opioid administration for an extended period of time, and
   - cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

6. Dose

   Doses must be individualized based upon the status of each patient and should be assessed at regular intervals after Duragesic® application. Reduced doses of Duragesic® are suggested for the elderly and other groups discussed in precautions.

   Duragesic® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

7. Route of Administration and Regimens

   Duragesic® (fentanyl transdermal system) should be applied to intact, non-irritated and non-irradiated skin on a flat surface such as chest, back, flank or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate application. Hair at the application site should be clipped (not shaved) prior to system application. If the site of Duragesic® application must be cleansed prior to application of the patch, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to patch application.

   Duragesic® should be applied immediately upon removal from the sealed package. Do not alter the patch (e.g., cut) in any way prior to application and do not use cut or damaged patches.

   The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges. If the gel from the drug reservoir accidentally contacts the skin of the patient or caregiver, the skin should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin.

   Each Duragesic® is to be worn continuously for 72 hours. The next patch should be applied to a different skin site after removal of the previous transdermal system.

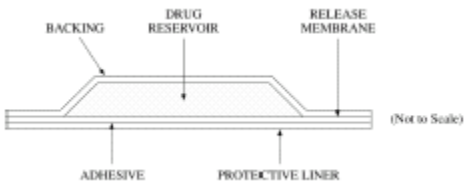
8. Description of the reference drug

   Duragesic® is a prescription drug available in 5 strengths (see table below for details). It is supplied in cartons containing 5 individually packaged systems. Duragesic® is for use only in opioid tolerant patients.

Duragesic® Dose (mcg/hr)	System Size (cm^2)	Fentanyl Content (mg)
Duragesic®-12.5	5	1.25
Duragesic®-25	10	2.5
Duragesic®-50	20	5
Duragesic®-75	30	7.5
Duragesic®-100	40	10

Duragesic® is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of polyester film;
2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose;
3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and
4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



Reviewer's comment: *The components of the test product are the same as those described in the labeling of the RLD except for the backing layer.*

9. Pertinent safety considerations

There is a 2-page box warning in the Duragesic® labeling emphasizing the risk of fatal overdose due to respiratory depression and the importance of using this product only in opioid tolerant patients.

C. Regulatory Background

1. INDs, Protocols, and/or Control Documents submitted by this sponsor

No INDs, Protocols, and/or Control Documents were submitted by this sponsor for this drug product regarding the skin irritation, sensitization and adhesion study. The sponsor made reference to the OGD's response to (b) (4) Control Document (OGD# 02-593).

2. INDs, Protocols, and/or Control Documents submitted by other sponsors

   Several protocols and controls have been submitted by other sponsors for this drug product.

3. Other ANDA submissions for same or related product

   There are four ANDAs (76-709, 76-258, 77-051 and 77-062) approved for generic versions of this drug product. There are also other ANDAs currently under review.

D. Other Relevant Information

Withdrawn Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999)

Reviewer's comments: *This guidance does not represent the most recent recommendations of the OGD, with regard to evaluation of this product.*

II. Description of Clinical Data and Sources

"A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Healthy Adult Subjects" (Protocol 770-0407-01)

A. CRO PRACS Institute, Ltd.
15222-B Avenue of Science
San Diego, CA 92128

B. Study Period
1. Screen: July 19, 2004
2. Study Period (First dose to last visit): July 20, 2004 to August 10, 2004

C. Study Centers, Investigators and Enrollment
Study Center: PRACS Institute, Ltd., San Diego, CA
Principal Investigator: Robert A. Harper, Ph.D.
Enrollment: 37 subjects

"Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects" (Protocol 770-0407-03)

A. CRO PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58106

B. Study Period
1. Screen: August 2, 2004 to August 6, 2004

2. Study Period: August 9, 2004 to September 20, 2004

C. Study Centers, Investigators and Enrollment

Study Center: PRACS Institute, Ltd., Fargo, ND
Principal Investigator: Alan K. Copa, Pharm.D.
Enrollment: 220 subjects

"A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 mcg/hr) Compared to Duragesic® (Fentanyl Transdermal System) 25 mcg/hr Patches" (Protocol 770-0407-02)

A. CRO Novum Pharmaceutical Research Services, Pittsburg, PA

B. Study Period

Dosing Dates: July 23, 2004 and August 6, 2004

C. Study Centers, Investigators and Enrollment

Study Center: Novum Pharmaceutical Research Services, Pittsburg, PA
Principal Investigator: Shirley Ann Kennedy, M.D.
Enrollment: 36 subjects

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

1. Original Submission:
   Original Submission dated December 17, 2004

2. Study Amendments
   Bioequivalence Amendment dated April 20, 2005
   Bioequivalence Amendment dated June 15, 2005
   Bioequivalence Amendment dated January 31, 2007
   Bioequivalence Amendment dated August 30, 2007

3. NDA #19-813 Original reviews of clinical trials.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations Report

A request for investigation was submitted on August 8, 2005. DSI conducted two clinical site inspections (EIR review dated September 7, 2006). One site (Fargo, ND) has been classified as NAI (no Action Indicated). The second site (San Diego, CA) has been classified as VAI (Voluntary Action Indicated). During the inspections, DSI issued FDA Form 483 for failure to follow the protocol. The deficiency is further described on page 47 of this review.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the study report, these studies were conducted in accordance with the Declaration of Helsinki, up to and including the most recent amendments. These studies were also conducted in accordance with Good Clinical Practice (GCP) as contained in the US Code of Federal Regulations governing the protection of human subjects (Title 21, Part 50), IRBs (Title 21, Part 56), and the obligations of clinical investigators (Title 21, Part 312).

Protocol 770-0407-01 and the informed consent form (ICF) were approved by the (b) (4) Investigational Review Board on July 14, 2004. Protocol 770-0407-03 and the ICF was approved by the PRACS Institute, Ltd Institutional Review Board on August 3, 2004. Protocol 770-0407-02 and ICF were initially reviewed and approved by the Novum Independent Institutional Review Board (NIIRB) on July 6, 2004. Subsequent to this approval, revisions to ICF and amendments to the protocol were made and approved by NIIRB.

D. Evaluation of Financial Disclosure

The sponsor certified that the investigators involved in these studies did not have any financial arrangements, significant payments, proprietary interest or equity interest to report.

IV. Review of Skin Sensitization, Irritation, and Adhesion

A. Brief Statement of Conclusions

The data submitted to ANDA 77-449 are sufficient to demonstrate that the **skin irritation potential** of the Teva placebo fentanyl transdermal system (TDS) is no worse than that of the positive controls (0.02% and 0.04% sodium lauryl sulfate) of low irritancy. The data also demonstrate minimal potential of the placebo fentanyl TDS to induce **sensitization** as would be expected with use of the RLD, Duragesic®. The data also demonstrate that the **adhesive performance** of the Teva fentanyl TDS is at least as good as that of the RLD.

B. General Approach to Review of the Comparative Skin Sensitization, Irritation, and Adhesion Data

The sponsor conducted two clinical studies and one pharmacokinetic study.

The first clinical study (Protocol 770-0407-01) was reviewed to evaluate the irritation and adhesion properties of the proposed generic fentanyl TDS. The second clinical study (Protocol 770-0407-03) was reviewed to evaluate the sensitization, irritation and adhesion properties of the proposed generic fentanyl TDS.

The pharmacokinetic study (Protocol 770-0407-02) was reviewed to evaluate the adhesion properties of the proposed generic fentanyl TDS. The review of the pharmacokinetic data was conducted by the Division of Bioequivalence and is reported separately.

The paper submissions of the ANDA as well as the electronic submissions were reviewed in detail.

C. Detailed Review of Skin Sensitization, Irritation, and Adhesion Studies

"A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Healthy Adult Subjects" (Protocol 770-0407-01)

1. **Sponsor's protocol**: 770-0407-01

2. **Title**: A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System in Healthy Adult Subjects

3. **Objective**: The primary objective was to assess the cumulative irritation potential of a placebo TDS compared to that of the positive control product intended to provoke "mild" irritation, (sodium lauryl sulfate) and a negative control (0.9% sodium chloride) using a 21-day cumulative irritation study design. The secondary objective was to assess adhesion of the placebo 25 mcg/hr fentanyl TDS prior to removal at every visit.

4. **Study Design**:
   This was a partially blinded, randomized study using a within-subject randomized design where each subject received all test materials. The study consisted of a screening period and a 21-day application period.

   a. Treatments

Test Article Code	Description
A	Placebo 25 mcg/hr fentanyl TDS (10cm^2)
B	Negative irritant control - saline (0.9%, sodium chloride)
C	Positive irritant control 1 - SLS, 0.02%; anionic surfactant
D	Positive irritant control 2 - SLS, 0.04%; anionic surfactant

The patch system for the controls was made from a nonwoven cotton pad ((b) (4)) (approximately 1.8 cm x 1.8 cm) covered by and secured on all sides by an occlusive hypoallergenic tape (approximately 3.8 cm x 3.8 cm). The SLS was made by weighing (weight by volume) the appropriate amount of solid SLS into a dry 100 ml volumetric flask. Fresh solutions were prepared every seven days. Control solutions (0.2 ml) were applied via pipette directly to patch pads and immediately applied to the skin.

Reviewer's Comments:

- *This patch is intended for 72 hours of continuous wear. Furthermore, addition of the active drug could change the adhesive performance of the patch. Therefore, data*

from this placebo study provides only supportive information on the adhesive performance of the proposed product.

b. Study population

i. Inclusion Criteria
Subjects participated if they met all of the following criteria:
(a) Female or male, ages 18 to 65
(b) Good general health as determined by a medical investigator
(c) Signed an informed consent

ii. Exclusion Criteria
(a) Insulin dependent diabetes
(b) Pregnant or lactating
(c) Asthma requiring chronic or frequent medication
(d) Immunological disorders such as HIV positive, AIDS, rheumatoid arthritis, and systemic lupus erythematous
(e) Treatment of any type of cancer within the last six months
(f) Use of immunosuppressive drugs including systemic and topical corticosteroids within 3 weeks of study enrollment
(g) Routine use of anti-inflammatory medication (including Ibuprofen and Celebrex)
(h) Use of systemic or topically applied analgesics or antihistamines within 72 hours of study enrollment except acetaminophen and aspirin (≤ 650 mg/day)
(i) Use of topical drugs at patch site
(j) Clinically significant skin diseases which may contraindicate participation, including psoriasis, eczema, atopic dermatitis, and active cancer
(k) Damaged skin in or around test sites which include sunburn, extremely deep tans, uneven skin tones, tattoos, scars or other disfiguration of the test site
(l) Participation in any patch test for irritation or sensitization within the last four weeks
(m) Current participation in any clinical testing, including other studies being conducted at PRACS Dermatology, LLC, or PRACS Institute Ltd.
(n) Known sensitization to medical adhesives or other components of the test articles
(o) Medical conditions which, in the Investigator's judgment, make the subject ineligible or place the subject at undue risk

c. Procedures/Observations

During the application period, one (1) transdermal system was applied during each clinic visit plus one (1) occluded patch containing 0.2 ml of saline (0.9% sodium chloride), and two (2) occluded patches containing sodium lauryl sulfate at 0.02% and 0.04%. Placebo TDS and control patches were placed on the upper paraspinal quadrants of the back. The same application site was used each day for each system. If a significant irritation developed (dermal response grade ≥ 3 or a surface score of grade F, G, or H), the site of the irritation was discontinued from use. The sites of application for each volunteer were randomized among placebo system, negative control, and the positive controls.

The test articles were applied daily for 21 days at approximately the same time each day and remained in place for 24 ± 1 hour. Subjects were instructed to leave the test articles in place and keep the patches dry. Subjects were allowed to shower with the patches in place. Subjects were also instructed to note the time of day if a patch fell off or was removed by the subject prior to the clinic visit. No auxiliary tape was applied during the study to maintain patch adhesion.

The application site was cleansed gently with warm water and thoroughly dried at least 15 minutes prior to the first patch application. The application sites were wiped gently with a moist tissue following system removal and reaction grading on each subsequent application day. Subjects were not allowed to wash the application sites with soaps or apply any lotions to the application sites during the study.

Table A.1: Study Schedule

Visit/Study Day	Screen	Day 1	Day 2 to 21	Day 22
Obtain Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History	X			
Pregnancy Test	X			
Test Article Applications		X	X	
Adhesion Evaluation			X	X
Test Article Removal			X	X
Skin Reaction Evaluation			X	X
Assess AE's	X	X	X	X
Concomitant Medication	X	X	X	X
Deviation Documentation	X	X	X	X

d. Restrictions

i. Prior and Concomitant Therapy
Subjects were instructed not to take any prescription medications (except those allowed by the protocol) without prior consultation with a Clinical Investigator.

Reviewer's comments: *None of the subjects were on any restricted concomitant medication.*

e. Removal of Subjects from Therapy or Assessment

Subjects were discontinued from the study for the following reasons:
i. Intolerance to a required study procedure at any time point.
ii. Noncompliance with protocol restrictions and requirements (e.g., failure to remain at the test facility for the duration of the evaluation period) at any time point.
iii. The occurrence of a serious adverse event experienced at any time point.
iv. Subject withdrawal of consent at any time point.

Reviewer's comments: *If a patch for a subject was discontinued due to intolerable irritation then that particular patch for the subject should be included in the irritation analysis using the LOCF for the last score prior to discontinuation. The adhesion scores up to the discontinuation date for that particular patch should be included in the adhesion analysis. If possible, the other patches for the same subject should also be included in the relevant analyses.*

f. Endpoints

i. Dermatologic Evaluations (Cumulative Irritation)

The same individual conducted all scoring of test sites. The irritation scoring scale was that of Berger and Bowman.[1] A score was awarded when at least 25% of the patch area demonstrated a clinically significant skin response. A score consisted of a numeric grade that may be appended with a letter grade. An individual application site was discontinued from further application if irritation of ≥ 3 was present in the dermal response score, or if an F, G, or H in the surface score was obtained.

Reviewer's comments: *Presence of a clinically significant effect should not have been restricted to a minimum area of the patched site. Any reaction, regardless of the percentage of patched area, should have been noted. The sponsor did not indicate if any reactions occurred within <25% of the test article site. However, in this case, the patch has a matrix design, with homogeneous distribution of the ingredients. Therefore, it is not likely that a specific component of the patch could represent <25% of the surface area, as could be the case with an adhesive rim on a reservoir patch.*

Dermal Response:

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible, minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

[1] Berger, R.S., Bowman, J.P. (1982). A Reappraisal of the 21-Day Cumulative Irritation Test in Man. J. Toxicol. Ot. & Ocular Toxicol., 1(2);109-115.

Surface Effects:

A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
F	Glazing with fissure
G	Film of dried exudates covering all or part of the patch site
H	Small petechial erosions and/or scabs

ii. Adhesion Evaluations

Adhesion evaluations were conducted on all study visits immediately prior to removal of the placebo test article. The same individual conducted all scoring of test sites. An estimate of the adherence of the topical patch was rated as follows:

0 = ≥90% adhered (essentially no lift off of the skin)
1 = ≥75% to <90% adhered (some edges only lifting off of the skin)
2 = ≥50% to <75% adhered (less than half of the system lifting off the skin)
3 = >0% to <50% adhered, but not detached (more than half the system lifting off of the skin without falling off)
4 = 0% adhered - test system detached (test system completely off the skin)

Reviewer's comment:
Adhesion evaluations were reported only for Test Article A (placebo Fentanyl TDS). Therefore, proper adhesion of the other test articles in order to induce maximal irritation potential cannot be verified.

g. Statistical analysis plan

i. Patient Population

Not provided by the sponsor.

Reviewer's comments:
The statistical analyses for adhesion and cumulative irritation comparisons should have separately defined analysis populations (the Per-Protocol populations), other than the safety population. These populations should be based on individual test articles (e.g., Patch A, Patch B, etc.) and not based on individual subjects.

- *The PP populations for adhesion should only include those patch applications per test article:*
  - *for subjects who met inclusion/exclusion criteria,*
  - *for subjects who did not violate protocol,*
  - *that were not discontinued due to irritation*
  - *within visit window (± 8 hours)*

- *The PP populations for cumulative irritation should only include those test articles for subjects:*
    - *who met inclusion/exclusion criteria,*
    - *did not violate protocol*
    - *within visit window (± 8 hours)*
    - *completed the study*
    - *for whom the test article was applied sequentially to the same site for the entire 3 weeks or who had the test article removed due to intolerable irritation, using LOCF*
    - *for whom the test article was not detached for any period longer than 24 hours, except those removed for excessive irritation*

ii. Adhesion

Frequency distributions of adhesion scores are presented for each evaluation time. No statistical analysis of this data was performed by the sponsor.

iii. Cumulative irritation

The source data is the actual patch test scores recorded following visual evaluation of the test sites. Only data from subjects who did not miss a visit were included in the analysis. One subject failed to return after visit 6. The subject was dropped from the study and data for this subject was excluded. In the event of a lost patch, the actual score recorded for the skin site was used in the statistical analysis. Subjects that withdrew from the test and subjects who experienced a reaction unrelated to the test article (coded as XR) were not included in the analysis.

The actual patch test scores were a combination of a numerical and a letter score consistent with the definitions given in the scoring scale. Scores containing letter grades were converted to numerical equivalents as follows: A = 0, B = 1, C = 2, and F, G, and H = 3. These equivalents were considered additive to any numerical score (e.g., 2C = 2 + 2 = 4). An upper limit of 3 was selected.

The transformed patch test scores observed during the cumulative irritation study for the test scores observed during the cumulative irritation study for the test articles were evaluated using the Friedman rank sum test. The overall total score for each test article was ranked within each subject and then analyzed using the Friedman rank sum test. The hypotheses for this test were as follows:

H_0: The rank sums of the test articles are identical.
H_a: At least two of the rank sums differ.

The Fishers LSD test 8 was performed if significant differences ($p < 0.05$) were observed within the Friedman rank sum test.

All statistical tests of hypothesis will employ a level of significance of 0.05.

Reviewer's comments:

- *If a patch was discontinued due to irritation score reaching ≥3 then LOCF of the last observed score should be carried forward for all the remaining observations of the study period for that particular test article.*
- *An upper limit of 3 is designated for discontinuing a patch from further application, the actual observed score should not be truncated at 3.*

Base 10 Categorization[2]

According to the sponsor, cumulative scores for the total panel and for base N=10 subjects were derived by application of the following formulae:

$$\text{Total Score (T.S.)} = \sum_{i=1}^{21} \sum_{j=1}^{N} \text{Sij}$$

Total Score for 10 Subjects (T.S.10) = (10)(1/N)(T.S.) where S_{ij} is the irritation score for the i^{th} application for the j^{th} subject and N is the total number of subjects for the i^{th} day for any one treatment.

These scores (S_{ij}) refer to reactions obtained with repeated applications to the same site or to scores carried forward for the same site after irritation reached the maximum limits allowed in the test.

For the calculation of total score, an upper limit of S_{ij}=3 was selected. Thus, for any value of S_{ij}>3, a value of 3 was entered into the formula for calculating total irritation scores. Also, following the development of a strong reaction, after application at the reaction site has been terminated, a value of 3 was entered for S_{ij} for all scorings for the remainder of the test.

According to the sponsor, the irritation of each test material was classified according to an empirically derived categorization system that was developed through experience with cosmetic articles. The interpretation and categorization system emphasized the comparative evaluation of relatively mild test materials. This measure attempts to predict responsiveness of a typical subject. It assumes the test panel is large enough to extrapolate to the population at large and the majority of the population would generally react in like manner and show comparative irritation profiles with the test panel under similar test conditions.

The following classification system was used to standardize the interpretation of Irritation Scores:

[2] *Berger, R.S., Bowman, J.P. (1982). A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol. Cut. & Ocular Toxicol. 1(2);109-115.*

Class	Score	Indications from Test	Description of Observed Responses
1	0-49	Mild article – no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e., continuous reapplication and occlusion at concentration specified).
2	50-199	Probably mild in normal use	Evidence of a slight potential for very mild cumulative irritation under conditions of test.
3	200-449	Possibly mild in normal use	Evidence of a moderate potential for mild cumulative irritation under conditions of test.
4	450-580	Experimental cumulative irritant	Evidence of a strong potential for mild to moderate cumulative irritation under conditions of test.
5	581-630	Experimental primary irritant	Evidence of potential for primary irritant irritation under conditions of test.

The above classification was regarded as an attempt to differentiate the irritation potential of relatively mild test materials. It was a comparative evaluation system in that it was an experimental estimate based on a relatively small sample size and specific experimental patch application conditions.

Reviewer's comment: *The sponsor's statistical approach is different than that usually used for analysis of these data, particularly with regard to transformed scores and rank sums. The FDA statistician was requested to perform appropriate statistical analysis to determine the cumulative irritation potential of the placebo test article.*

5. Study Conduct

a. Discussion of compliance

Study personnel applied and removed all transdermal systems. At each return visit, all subjects were questioned regarding their compliance with the protocol and any adverse events since their previous visit.

b. Randomization/Blinding

i. To eliminate any position bias, the assignment of the test articles to the test sites were randomized among the subjects so that each test article occupied individual skin sites within the panel of test subjects with approximately equal frequency.
ii. The skin reaction evaluator was partially blinded to the skin site randomization of each subject and their previous scores. The term 'partially blinded' was used because the test articles were different in size and shape however; the trained skin evaluator was blinded to the identity of the test materials and blinded to any previous scores.

Reviewer's comments*: Due to differences in appearance of the patches, it is likely that blinding of the observer/evaluator was difficult, especially for evaluation of patch*

adhesion, which requires direct observation of the patch itself. However, efforts could have been made to blind the evaluation of irritation during this study.

c. Reserve Samples

Not applicable since only placebo transdermal patches were used during this study.

d. Patient population (number included/excluded)

This study enrolled thirty-seven (37) healthy male and female volunteers, of ages between 18-65 years with no medication use in the previous 14 days and judged to be healthy on the basis of pre-study examinations and tests. Thirty-six out of the 37 subjects enrolled completed the study.

***Reviewer's comments**:*

- *Since this is a placebo study, all adhesion data is considered as supportive information and is used to ensure adequate adhesion of the test articles to induce maximum irritation and sensitization potential.*
- *It should be noted that the sponsor's data does not indicate if and when a test article was discontinued from further applications due to excessive irritation. However, according to this reviewer's evaluation of the sponsor's dataset, none of the subjects reached an irritation score of 3 for Test Article A (placebo daily patch change).*
- *FDA **Irritation** PP Exclusions - The following test articles per subject need to be excluded (and LOCF should not be used unless specified) from the PP Irritation population:*
    - *Based on the data provided by the sponsor, it appears that Subject 337 discontinued early from the study. According to the study report, the subject failed to return after visit 6. No scores are provided for Subject 337.*
    - *Subject 308: On 7/25/04 test article B was inadvertently patched on the incorrect application site. The patch was removed within 30 seconds, and the site was washed with distilled water and cotton balls. The subject was repatched with the correct test article after the site had dried.*
    - *The following patch applications for these subjects' test articles were detached, however, they were NOT detached for more than 24 hours (therefore, these do not need to be exclude from the PP population for irritation analysis for this reason):*
        - *Test Article A (Placebo): subject 309 (application number 7); 313 (5); 317 (4, 7 and 20); 319 (20)*
    - *Adequate patch adhesion of the other test articles could not be verified due to the sponsor not reporting this data. If the control patches did not adhere well, the risk would be more irritation potential for the controls than what was observed. Therefore, the test placebo would be relatively less irritating in comparison.*

6. Results

a. Adhesion

According to the sponsor, adhesion scores varied from day to day with 69% of the subjects having greater than 90% adherence on score Day 1 to 97% on score Day 9, 12, 18 and 19. Overall, an average of 90.34% of the subjects had greater than 90% adhesion of the TDS during the course of the study. A total of six subjects on four different score days had the test system totally detached when arriving at the test facility. A total of three subjects on two different score days had less than 50% adherence of the TDS. A total of eight subjects on seven score days had greater than 50% to less than 75% adherence of the TDS. A total of fifty-six subjects on 19 score days had greater than 75% to less than 90% adherence of the TDS.

Table A.2 – Percent of Subjects with Adhesion Scores – Test Article A – Placebo Fentanyl TDS Daily Patch Changes (per Sponsor)

Application Day	Total of Scores				
	0	1	2	3	4
1	69.44%	27.78%	2.78%	0.00%	0.00%
2	88.89%	11.11%	0.00%	0.00%	0.00%
3	75.00%	22.22%	2.78%	0.00%	0.00%
4	88.89%	5.56%	2.78%	0.00%	2.78%
5	91.67%	2.78%	0.00%	2.78%	2.78%
6	94.44%	2.78%	2.78%	0.00%	0.00%
7	86.11%	5.56%	0.00%	2.78%	5.56%
8	91.67%	8.33%	0.00%	0.00%	0.00%
9	97.22%	0.00%	0.00%	2.78%	0.00%
10	83.33%	13.89%	2.78%	0.00%	0.00%
11	91.67%	8.33%	0.00%	0.00%	0.00%
12	97.22%	2.78%	0.00%	0.00%	0.00%
13	94.44%	5.56%	0.00%	0.00%	0.00%
14	94.44%	5.56%	0.00%	0.00%	0.00%
15	91.67%	2.78%	5.56%	0.00%	2.78%
16	94.44%	5.56%	0.00%	0.00%	2.78%
17	88.89%	8.33%	2.78%	0.00%	0.00%
18	97.22%	2.78%	0.00%	0.00%	5.56%
19	97.22%	2.78%	0.00%	0.00%	0.00%
20	94.44%	0.00%	0.00%	0.00%	0.00%
21	88.89%	11.11%	0.00%	0.00%	0.00%

Reviewer's comments:

- *Because the fentanyl transdermal system is intended to be worn for 72 hours, the adhesion results of this study provide little useful information. Therefore, the FDA statistician was not requested to analyze the adhesion data from this study.*
- *The NDA summary of all the clinical studies for the RLD does not mention how many patches fell off during the study period.*

b. Irritation

According to the sponsor, the placebo TDS produced a Base 10 irritation score of 140.83, identical to the Base 10 score for the 0.02% SLS positive control, and less than the 0.04% SLS positive control. A Base 10 score represents a Class 2 response, probably mild in normal use, evidence of slight potential for very mild cumulative irritation. The Base 10 score for the negative control, saline, was 37.22, which represents a Class 1 response, mild article, no experimental irritation in normal use, essentially no evidence of cumulative irritation. The high SLS control gave a Base 10 score of 330.83, which represents a Class 3 response, possibly mild in normal use, evidence of moderate potential for mild cumulative irritation.

Statistically significant differences among test articles were observed with the Friedman rank sum test ($p < .0001$). The Fishers LSD Test 8 determined that there were statistically significant differences among the Placebo, the negative control and the 0.04% SLS positive control ($p < 0.01$). However, there was no statistically significant difference between the Placebo and the 0.02% SLS positive control ($p > .05$).

Sponsor Code	Score Response, Base 10	Class	Indication from Test	Description of Observed Responses
A–Placebo TDS	140.83	2	Probably mild in normal use.	Evidence of slight potential for very mild cumulative irritation
B–saline negative control	37.22	1	Mild article – no experimental irritation in normal use.	Essentially no evidence of cumulative irritation
C–low (0.02%) SLS positive control	140.83	2	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation
D–high (0.04%) SLS positive control	330.83	3	Possibly mild in normal use.	Evidence of moderate potential for mild cumulative irritation

***Reviewer's comments**:*

- *The sponsor's data does not indicate if and when a test article was discontinued from further applications due to excessive irritation or due to tape irritation. In addition, it appears that discontinued test article application sites were continued to be scored after test article discontinuation. These residual irritation scores are not indicated in any way within the electronic datasets.*
- *The FDA statistician was requested to provide a frequency table of irritation scores for each test article on each study day. A calculation of mean irritation scores for each test article was also requested. The relevant statistical analysis for the irritation evaluation is the upper bound of the one-sided 95% CI of the difference in mean irritation score for A (placebo TDS) minus 1.25 times the mean score for D (the 0.04% SLS positive control), which must be less than or equal to zero to support approval of the application. The results of the FDA statistician's analyses are provided below in Tables A.3, A.4 and A.5.*

Table A.3 - Frequency of individual total irritation scores per each patch* per observation *(per FDA Statistician)

Patch	Total Score						Total number of scores
	0	1	2	3	4	5	
Test placebo	285	431	40				756 (30x21)
Negative control	628	122	6				756 (30x21)
Positive control (0.02%)	283	440	29	2		2	756 (30x21)
Positive control (0.04%)	85	177	168	298	6	22	756 (30x21)

Table A.4 - Frequency of maximum total irritation scores per each patch* per subject *(per FDA Statistician)

Patch	Total Score						Total number of subject
	0	1	2	3	4	5	
Test placebo	3	27	6				36
Negative control	16	17	3				36
Positive control (0.02%)		27	8			1	36
Positive control (0.04%)		1	1	24		10	36

Table A.5 - Analysis result for mean total irritation score using the mixed model Test placebo versus Negative and Positive controls (per FDA Statistician)

Comparator	LS mean (A: Test placebo)	LS mean (Comparator)	Upper limit one-sided 95% CB (T-1.25 B)	Pass the Non-Inferiority Test?
Negative control	0.6759	0.1772	0.5722	No
Positive control (0.02%)	0.6759	0.6799	-0.05406	Pass
Positive control (0.04%)	0.6759	2.0384	-1.7057	Pass

c. Discontinuation of Patch

Not provided by the sponsor.

Reviewer's comments:

- *The sponsor's electronic data does not indicate if and when a test article was discontinued early due to excessive irritation. It appears that such an event is noted*

only in the CRF of each subject. However, according to this reviewer's evaluation of the sponsor's dataset, none of the subjects reached an irritation score of 3 for Test Article A (placebo daily patch change).

- *The NDA summary of all the clinical studies for the RLD does not mention how many patches had to be discontinued due to irritation.*

"Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects" (Protocol 770-0407-03)

1. **Sponsor's protocol#** 770-0407-03

2. **Title:** Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects

3. **Objective**

   a. Primary objective: To evaluate the potential of the placebo 25 mcg/hr fentanyl transdermal delivery system (TDS) for contact sensitization using the guidance for Industry as provided by the FDA for skin irritation and sensitization testing for transdermal drug products, which is a modification of the standard Draize test.

   b. Secondary objective: To assess adhesion of the placebo 25 mcg/hr fentanyl TDS prior to removal at every visit.

4. **Study Design**

   This study was a single-center, single blinded study using a within-subject randomized design where each subject received all test materials. The study consisted of a three-week induction period, an approximate two-week rest period, and a one-week challenge period.

   a. Treatments

Test Article Code	Description
A	Placebo 25 mcg/hr fentanyl TDS (10.7cm^2)
B	Negative irritant control - Normal saline (0.9% aqueous sodium chloride)

   The patch system for the control was made from a nonwoven cotton pad ((b) (4)), approximately 1.8 cm x 1.8 cm, covered by and secured on all sides by an occlusive hypoallergenic tape (approximately 3.8 cm x 3.8 cm).

   Reviewer's comments:

   - *Addition of the active drug could change the adhesive performance of the patch. Therefore, data from this placebo study provide limited adhesion information.*

- *The irritation data, without direct comparison to a positive irritant control, during the induction phase provides little useful information on the cumulative irritation potential.*

b. Study population

i. Inclusion Criteria
Same as Study 770-0407-01

ii. Exclusion Criteria
Same as Study 770-0407-01

c. Procedures/Observations

i. Induction Period

Subjects who missed a visit during the induction period were allowed a make-up visit at the end of the induction period. A maximum of one (1) placebo test article and one (1) negative control article were applied to each subject by study personnel. Nine repetitive applications (three patch applications per week) of the test articles were applied to the same site (paraspinal region of the upper back) for approximately 48 or 72-hour (±2 hours) exposure per application. Scoring for adhesion was performed immediately prior to removal at every visit by qualified study personnel. Scoring for irritation during this phase of the study was done immediately prior to reapplication. No auxiliary tape was used on the patches to maintain adhesion.

ii. Rest Period

Following the three-week induction period, subjects did not receive any application of test articles for approximately 14-17 days.

iii. Challenge Period

A challenge patch application occurred 14 to 17 days following the final induction visit (final patch removal). The transdermal patch and the negative control patch were applied for 48 ±2 hours to naïve sites located away from the original application sites. Patch adhesion was assessed before patch removal. Patches were removed by the study site staff and the test sites evaluated approximately 30 minutes, and again at 24±1 hours, 48±2 hours and 72±2 hours after patch removal.

iv. Re-Challenge Period

Positive reactions, at challenge, are generally more intense and persistent than reactions noted during the induction period, particularly those noted early in the test. Characteristically, they are eczematous (papulovesicular, edematous) rather than strictly erythematous with surface damage. These comparisons, however, are not

always diagnostic and borderline or suggestive responses in this study were to be re-challenged.

Re-challenges, were to be conducted at least 2-4 weeks after resolution of the original reactions, in order to avoid the conditioned response ("angry-back syndrome"). The immune response retained its specificity and sensitivity for an extended period, whereas hyperirritability should subside. This re-challenge would consist of the application of the placebo test article for an approximate 48-hour exposure to a naïve site to confirm reactions indicative of contact sensitization.

Table B.1 - Standard Induction Period

		Induction Period										
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Make up[1]**
Study Day	**-14-0**	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**19**	**22**	**24**
Obtain Consent	X											
Inclusion/Exclusion Criteria	X											
Medical History	X											
Test Article Application		X	X	X	X	X	X	X	X	X	X[1]	
Pregnancy Test		X										
Adhesion Evaluation			X	X	X	X	X	X	X	X	X	X
Test Article Removal			X	X	X	X	X	X	X	X	X	X
Skin Reaction Evaluation			X	X	X	X	X	X	X	X	X	X
Assess AE's	X	X	X	X	X	X	X	X	X	X	X	X
Deviation Documentation	X	X	X	X		X		X	X	X	X	X
Concomitant medication use	X	X	X	X	X	X	X	X	X	X	X	X

[1] Procedures or visit only required for subjects missing one visit.

Table B.2 - Rest and Challenge Period

Activity	**Rest Period**	**Challenge Period**					
	Day	**Hours Post Application**		**Hours Post Removal**			
Study Day/Challenge Hours	**22-39**	**0**	**48**	**0.5**	**24**	**48**	**72**
Pregnancy Test		X					
Test Article Application		X					
Test Article Removal			X				
Skin Reaction Evaluation			X	X[1]	X	X	X
Assess AE's		X[3]	X		X	X	X
Deviation Documentation		X	X		X	X	X
Concomitant medication use		X[2]	X		X	X	X
Termination Sheet							X

[1] Skin Reaction Evaluations at this visit are conducted approximately 30 minutes after placebo test system removal.
[2] Adverse events experienced and used of concomitant medication during the Rest Period will be recorded.
[3] To be completed at the final visit or at any time the subject is prematurely discontinued.

d. Restrictions

Same as Study 770-0407-01

e. Removal of Subjects from Therapy or Assessment

Same as Study 770-0407-01

f. Endpoints

i. Dermatologic Evaluations (Skin Assessment)

A score was awarded when at least 25% or more of the patch area demonstrated a clinically significant skin response. A score consisted of a numeric grade that may be appended with a letter grade and/or an additional observation grade. In instances where a strong reaction warranted application of the test article to the M or M-1 site, residual scores were recorded through to the end of the study for all previously exposed sites.

Reviewer's comments:

- *The sponsor did not define in the protocol or the study report what would constitute a "strong reaction" that would lead to the discontinuation of an application site.*
- *Residual scores from discontinued application sites should not be used in any of the statistical analyses.*
- *Presence of a clinically significant effect should not have been restricted to a minimum area of the patched site. Any reaction, regardless of the percentage of patched area, should have been noted. The sponsor did not indicate if any reactions occurred within <25% of the test article site.*

Reactions to the test materials were scored as follows:

0	No visible reaction or erythema
1	Mild reaction, macular erythema (faint, but definite pink)
2	Moderate reaction, macular erythema (definite redness, sunburn appearance)
3	Strong to severe reaction, macular erythema (intense redness)

Definition of letter grades appended to a numerical grade:

E	Edema (swelling, spongy feeling when palpated)
P	Papule (red, solid, pinpoint elevations, granular feeling, <5 mm diameter)
V	Vesicles (fluid-filled lesion <5 mm diameter)
B	Bulla (fluid-filled lesion >5 mm diameter)
S	Spreading (evidence of the reaction beyond the patch area)
W	Weeping (serous exudates, clear fluid oozing or covering patch site)
I	Induration (solid, elevated, hardened, thickening skin reaction)

The effects on superficial layers of the skin were scored as follows:

g	Glazing
p	Peeling
c	Scab, dried film of serous exudates
d	Hyperpigmentation, reddish-brown discoloration
h	Hypopigmentation, loss of visible pigmentation
f	Fissuring, grooves in the superficial layers of the skin

Symbols Used in Tabulating Data and/or Deviations:

O	Original application site
M	Adjacent site (application following strong reaction during induction)
M-1	Second adjacent site
A	Naïve adjacent site used during challenge application
X	Patch omitted due to previous strong reaction
XR	Patch omitted for reasons unrelated to the test material
L	Test patch worn less than 23 hours
--	Subject absent
DR	Subject dropped from study
(C)	Comments included below or on supplemental information page

Reviewer's comments: *The sponsor did not define* a priori *what would constitute a sensitization reaction. According to the Draize Method (as outlined in "The Use of Graded Concentrations in Studying Skin sensitizers: Experimental Contact Sensitization in Man" Fd Cosmet. Toxicol pp.219-227), a subject is considered sensitized/positive during the challenge phase if the skin reaction is graded as ≥2 (where 1 = erythema; 2 = erythema and induration; 3 = vesiculation and; 4 = bulla formation).*

Using the sponsor's sensitization reaction scale, the definition of sensitization given by the Draize Method would be equivalent to any numerical score ≥1 AND the presence of any letter score. If the subject had a score of ≥1 and a score with a letter (other effects), then that subject's reaction is likely a sensitization reaction. In addition, the course of the reaction over a 24- to 72-hour period should be considered to determine if the reaction is a sensitization reaction. If the subject had a score of 1 or greater during the early post-removal time points (30 minutes, 24 hours) but resolved at the later time points (48, 72 hours), then that patient should be deemed to have had an irritation reaction. If the scores persisted, then the induction scores should be analyzed to determine if they were similar to the challenge scores. If the subject also had similar scores during the initial induction period, then that should also be deemed an irritation reaction. If the scores were significantly higher than the induction scores and persisted until the 72 hours, then that patient should be seen as a likely candidate for a sensitization reaction.

ii. Adhesion Evaluations

Same as Study 770-0407-01.

Adhesion assessments were performed by various personnel.

g. Statistical analysis plan

i. Patient Population:
Not provided by the sponsor.

Reviewer's comments:

- *The sponsor did not specify the Per-Protocol population* a priori.
- *The statistical analyses for adhesion and sensitization comparisons should have separately defined analysis populations (the Per-Protocol populations). These populations should be based on individual patches (e.g., Patch A, Patch B) and not based on individual subjects.*
- *The PP populations for* ***adhesion*** *should be based on individual patches per application and should only include those patch applications:*
  - *for subjects who met inclusion/exclusion criteria,*
  - *for subjects who received at least one 3-day patch application,*
  - *for subjects who did not violate protocol,*
  - *that were applied prior to being discontinued due to intolerable irritation, and*
  - *within visit window (as specified by the sponsor)*
- *The PP populations for* ***sensitization*** *analyses should be based on individual patches and should only include those patches for subjects:*
  - *who met inclusion/exclusion criteria,*
  - *received a defined number of patch applications (9 patches) during the induction period,*
  - *did not violate protocol,*
  - *did not have the patch detached for any period longer than 24 hours during the induction period,*
  - *who were within the visit window (as specified by the sponsor), and*
  - *completed the study.*

ii. Skin Sensitization Analysis

The interpretation of data was based on the pattern of reactivity of the test article during induction when compared to the severity and persistence of the reaction(s) observed at challenge. Increased reactivity noted during the first week of induction to test articles that are considered non-irritating or minimally irritating generally indicated a pre-sensitized condition. Comparable reactivity during the third week, if it appeared suddenly, was suggestive of the initiation of sensitization. Cumulative irritation generally developed more gradually and resolved with a comparable sequence after patch removal.

Positive reactions, at challenge, were generally more intense and persistent than reactions noted during the induction period, particularly those noted early in the test. Characteristically, they were eczematous (papulovesicular, edematous) rather than strictly erythematous with surface damage. These comparisons, however,

were not always diagnostic and borderline or suggestive responses were re-challenged.

Scores were tabulated. No statistical analysis was performed.

Reviewer's comments: *The sponsor did not convert letter scores to numerical scores.*

iii. Adhesion

Frequency distributions of adhesion scores were presented for each evaluation time. No statistical analysis of this data was performed.

5. Study Conduct

a. Discussion of compliance
Same as Study 770-0407-01

b. Randomization/Blinding
Same as Study 770-0407-01

c. Reserve Samples
Not applicable

d. Subject population (number included/excluded)
Two hundred twenty (220) subjects were enrolled into the study. According to the sponsor, two hundred ten (210) of the subjects completed the induction period of the study. Two hundred five (205) subjects completed the study and were included in the data analysis.

Subjects 65, 114 and 177 did not return for the challenge week. Subject 116 reported a pregnancy prior to the challenge phase and did not complete the study, exit procedures were performed and the pregnancy was followed until the birth. Subject 142 did not return for the 48 and 72 hour skin assessment visits during the challenge week.

Reviewer's comments*:*

- *Since this is a placebo study, all adhesion data is considered as supportive information and is used to ensure adequate adhesion of the test articles to induce maximum irritation and sensitization potential.*
- *FDA **Sensitization** PP Exclusions - The following subjects need to be excluded from the Sensitization population due to:*
  - *Subject was outside of the visit window: Subject 006 and 214*
  - *Patching error occurred where Patch A and B applications were switched for Subject 074.*
  - *Subject 004 had two Test Article B patches applied on 8/20/04. Test Article A was not applied.*

- *Protocol violation:*
  - *Subject 026 took diphenhydramine, acetaminophen (>650 mg/day), and naprosyn during the study*
  - *Subject 133 took ibuprofen during the study*
  - *Subject 116 became pregnant during the study and did not complete the challenge phase.*
- *Sunburn was noted on the back for Subject 210.*
- *The following subjects were "Dropped" from the study for various reasons. (The specific reasons are not provided in the datasets; however, it appears that the reasons are noted on the CRF.): Subjects 65, 69, 75, 90, 95, 114, 116, 169, 177, 178, 195, 213, 217, and 218*
- *For the following subjects, patches fell off during the induction period so that the subject was patch-free for a period of time (the sponsor did not provide the length of time prior to patch detachment in the datasets). These subjects may not have had 21 days of patch wear during the induction phase. These subjects should still be included in the PP population:*
  - *Test Article A: Subjects 1, 8, 11, 14, 43, 44, 51, 59, 60, 72, 78, 88, 89, 91, 94, 95, 104, 106, 107, 114, 116, 121, 122, 130, 132, 134, 139, 143, 145, 148, 152, 154, 155, 158, 163, 164, 172, 174, 179, 200, 201, 209, 210, and 213*
  - *Test Article B: Subjects 9, 11, 21, 24, 28, 31, 38, 46, 49, 52, 54, 59, 72, 74, 88, 89, 91, 94, 95, 101, 102, 106, 114, 116, 119, 122, 124, 126, 127, 132, 143, 145, 148, 152, 154, 158, 160, 162, 163, 175, 186, 189, 192, 200, 201, 205, 208, 210, 213, 216, and 220*
- *Patch falling off during the challenge phase: Subject 8, 10, 14, 19, 28, 30, 44, 89, 94, 106, 124, 126, 127, 148, 154, 158, 200, 208, 220*
- *Although the following subjects took acetaminophen (>650 mg/day), a protocol violation as outlined by to the sponsor's protocol, there is no need to exclude them from the PP population since acetaminophen is not an anti-inflammatory and should not confound the study outcome: Subjects 001, 055, 096, 101, 153, 155, 182, and 210*

6. Results

a. Skin Assessments

According to the sponsor, the placebo (fentanyl) TDS, 10.7cm^2, produced a total of 1968 skin reaction scores of "0" during the entire course of the study. This was in comparison to a total of 2346 scores of "0" for the control, 0.9% sodium chloride (saline). The placebo TDS produced a total of 675 scores of "1", mild reaction, while the saline control produced 290 scores of "1". Fourteen reaction scores of "2", moderate reaction, were produced by the placebo TDS during the study. There were only two reaction scores of "2" produced by the saline control. No reaction scores of "3", strong to severe reaction, were produced by the placebo TDS or the saline control. Only two scores of "E", edema, were produced by the placebo TDS, while the saline control produced no scores of "E". A total of 1197 scores of "P", papular reaction, were produced by the placebo TDS

compared to 382 scores of "P" produced by the saline control. There were 1347 scores of "g", glazing, produced by the placebo TDS compared to 83 scores of "g" produced by the saline control. Overall, the placebo fentanyl TDS produced more skin reactions than the saline control.

In terms of the ability of the placebo fentanyl TDS to induce sensitization, no reactions indicative of allergic contact dermatitis were seen in the induction or challenge phases of the study. Only six subjects had a score of "0P" at the 48 hour challenge evaluation and one subject had a score of "0P" at the 72 hour challenge evaluation. These reactions are not indicative of allergic contact dermatitis.

Table B.3 - Summary of Skin Assessment and Visual Evaluation Scores for Test Article A - Placebo Fentanyl TDS (per sponsor)

	Induction Period										Challenge Period				
	Application Day										Hours Post patch removal				
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**M/U**	**0.5**	**24**	**48**	**72**	**Sum**
0	135	81	28	5	5	7	2	3	2	0	132	184	198	204	986
1	49	30	5	1	0	2	1	0	1	0	17	0	0	0	106
2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0g	0	10	24	18	33	55	44	29	43	1	3	0	0	0	260
0p	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2
0P	16	43	27	8	2	3	3	1	0	0	40	16	6	1	166
0pg	0	0	0	0	0	1	3	1	2	0	0	0	0	0	7
0Pg	1	9	54	105	83	70	75	74	73	3	0	0	0	0	547
1g	0	8	11	5	9	11	14	16	15	2	0	0	0	0	91
1gE	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
1P	3	17	7	2	1	1	2	0	1	0	13	0	0	0	47
1pg	0	0	0	0	4	1	0	0	0	0	0	0	0	0	5
1Pg	0	6	45	56	65	47	58	75	62	10	0	0	0	0	424
1Pp	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
2EPg	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
2g	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
2P	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
2Pg	0	0	1	2	1	1	1	3	0	1	0	0	0	0	10
NA	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
N9G	0	0	0	0	0	0	0	0	3	0	0	0	0	0	3
Sum	205	204	202	204	204	200	205	202	204	17	205	200	204	205	

Table B.4 - Summary of Skin Assessment and Visual Evaluation Scores for Test Article B - 0.9% Aqueous Sodium Chloride (per sponsor)

	Induction Period										Challenge Period				
	Application Day										Hours Post patch removal				
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**M/U**	**0.5**	**24**	**48**	**72**	**Sum**
0	175	153	137	129	113	118	133	111	110	7	179	190	201	205	1961
1	23	30	8	15	39	20	30	32	31	6	8	2	0	0	234
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-	0	1	3	1	1	5	0	3	1	0	0	5	1	0	21
0g	0	2	15	4	5	8	6	7	4	1	0	0	0	0	52
0p	0	0	0	3	2	1	3	1	2	0	0	0	0	0	12
0P	7	16	33	49	33	40	34	39	45	1	15	8	3	0	323
0pg	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
0Pg	0	0	2	2	3	2	0	1	3	0	0	0	0	0	13
1g	0	1	2	0	0	4	1	3	1	1	0	0	0	0	13
1gE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1p	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
1P	0	0	2	2	9	7	3	7	5	0	3	0	0	0	38
1pg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1Pg	0	1	0	0	0	0	1	1	0	1	0	0	0	0	4
1Pp	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2EPg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2P	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
2Pg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N9G	0	0	0	0	0	0	0	0	3	0	0	0	0	0	3
XR	0	1	1	0	0	0	0	0	0	0	0	0	0	0	2
Sum	205	204	202	204	204	200	205	202	204	17	205	200	204	205	

Reviewer's comments:

- *The sponsor only provided the raw data for the skin irritation effects observed during the induction phase. The sponsor did not provide a summary or conclusion regarding the skin irritation potential of the proposed product for this study.*
- *Given that positive controls were not used, the irritation scores from this study are of limited value in evaluating the irritation potential.*
- *No subject presented a score indicative of sensitization during the challenge phase.*
- *The FDA statistician was requested to provide a descriptive analysis of the sensitization data from the challenge phase. The statistician was asked to use this reviewer's definition of a sensitized reaction, as provided under "Endpoints" of this review, in order to identify subjects who are potentially sensitized for Test Article A and B.*
- *The FDA statistician was also requested to calculate the mean cumulative irritation scores during the induction period for a descriptive comparison of the placebo and negative control. There was no need to calculate the confidence intervals, since there was no positive control in this study, and no comparison to the negative control is needed for a decision regarding approval of the application.*

Table B.5 - Frequency distribution of sensitization score at Hour 48 and 72 in the challenge period (per FDA Statistician)

Hour	Patch	Score		Total
		0	0P	
48*	Test placebo patch	172	6 (63, 71, 147, 186, 207, 209)	178
	Negative control patch	175	3 (68, 77, 103)	178
72	Test placebo patch	178	1 (207)	179
	Negative control patch	179		179

*: Subject 117 missed visit at Hour 48

b. Adhesion (per sponsor)

According to the sponsor, adhesion scores for the placebo fentanyl TDS varied from day to day with 67.16% of the subjects having greater than 90% adherence on score Day 3 to 95.12% on the challenge week score day. The percentage of subjects having ≥ 75% to 90% TDS adherence ranged from 2.44% on the challenge score day to 20% on score Day 1. The percentage of subjects having ≥ 50% to 75% TDS adherence ranged from 0% on score Day 8 and the make-up day, to 4.48% on Day 3. The percentage of subjects having >0% to <50% adherence, but not detached, ranged from 0% on score Days 2, 4, the make-up day, and the challenge score day, to 2.45% on score Day 5. The percent of subjects who had 0% adherence at the time of evaluation ranged from 0% on the make-up day to 4.52% on score Day 9.

Table B.6 - Adhesion Score Frequency - Test Article A - Placebo Fentanyl TDS (per sponsor)

Total Scores	Application Day										
	1	2	3	4	5	6	7	8	9	Make up	Challenge
N	**205**	**204**	**201**	**204**	**204**	**197**	**205**	**202**	**199**	**17**	**205**
0	155	168	135	169	172	169	180	181	173	16	195
1	41	29	45	26	17	13	18	14	14	1	5
2	4	4	9	5	3	5	1	0	1	0	1
3	1	0	4	0	5	2	1	1	2	0	0
4	4	3	8	4	7	8	5	6	9	0	4

Table B.7 - Percent of Subjects with Adhesion Scores - Test Article A - Placebo Fentanyl TDS (per sponsor)

Total Scores	Application Day										
	1	2	3	4	5	6	7	8	9	Make up	Challenge
N	**205**	**204**	**201**	**204**	**204**	**197**	**205**	**202**	**199**	**17**	**205**
0	75.61	82.35	67.16	82.84	84.31	85.79	87.80	89.60	86.93	94.12	95.12
1	20.00	14.22	22.39	12.75	8.33	6.60	8.78	6.93	7.04	5.88	2.44
2	1.95	7.96	4.48	2.45	1.47	2.54	0.49	0.00	0.50	0.00	0.49
3	0.49	0.00	1.99	0.00	2.45	1.02	0.49	0.50	1.01	0.00	0.00
4	1.95	1.47	3.98	1.96	3.43	4.06	2.44	2.97	4.52	0.00	1.95

Reviewer's comment: *Since this is a placebo study, all adhesion data is considered as supportive information and is used to ensure adequate adhesion of the test articles to induce maximum irritation and sensitization potential.*

"A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 mcg/hr) Compared to Duragesic® (Fentanyl Transdermal System) 25 mcg/hr Patches" (Protocol 770-0407-02)

1. **Sponsor's protocol#** 770-0407-02

2. **Title:** A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 mcg/hr) Compared to Duragesic® (Fentanyl Transdermal System) 25 mcg/hr Patches

3. **Objective**
   The purpose of this study was to evaluate the relative bioavailability of the test formulation of fentanyl 25 mcg/hr transdermal patch with the already marketed reference formulation Duragesic® (fentanyl transdermal system) 25 mcg/hr patch (Janssen) in healthy adult subjects.

Reviewer's comments: *For the purpose of this review, only the adhesion data was evaluated. The pharmacokinetic data has been reviewed by the Division of Bioequivalence.*

4. **Study Design**
   This was a randomized, single-center, single-dose, two-way, crossover study.

   a. Treatments

Treatment	Description
Test (B)	Fentanyl 25 mcg/hr TDS Patch, Lot No. 77082; Manufacturing date 06/04 (Manufactured by Aveva Drug Delivery Systems, Inc.)
Reference (C)	Duragesic® (fentanyl transdermal system) 25 mcg/hr Patch, Lot No. 0323963; Expiration date 09/05 (Manufactured by Alza Corporation, Distributed by Janssen Pharmaceutical Products, L.P.)

   b. Study population

      i. Inclusion Criteria
         (a) Males and females, 18-45 years of age (inclusive) with a minimum body weight of 120 lbs and a Body Mass Index (BMI) of ≥18 or ≤30
         (b) Female subjects of child bearing potential must either abstain from sexual intercourse or use a reliable method of contraception for at least 30 days prior to dosing and during the duration of the study.

(c) Good health as determined by lack of clinically significant abnormalities in health assessments performed at screening.
(d) Signed and dated informed consent form.

ii. Exclusion Criteria
(a) If female, pregnant, lactating or likely to become pregnant during the study.
(b) History of allergy or sensitivity to fentanyl, other opioids, or history of any drug hypersensitivity or intolerance (including allergy to glues, adhesives or similar) which, in the opinion of the Investigator, would compromise the safety of the subject or the study.
(c) Significant history or current evidence of chronic infectious disease, system disorder or organ dysfunction.
(d) Presence of gastrointestinal disease or history of malabsorption within the last year.
(e) History of psychiatric disorders occurring within the last two years that required hospitalization or medication.
(f) Presence of a medical condition requiring regular treatment with prescription drugs (other than contraceptives).
(g) Use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days prior to dosing.
(h) Receipt of any drug as part of a research study within 30 days prior to dosing.
(i) Any history of treatment for drug or alcohol addiction.
(j) Donation or significant loss of whole blood (480 ml or more) within 30 days or plasma within 14 days prior to dosing.
(k) Positive test results for HIV, Hepatitis B surface antigen or Hepatitis C antibody.
(l) Positive test results for drugs of abuse at screening.
(m) Positive serum pregnancy test.
(n) Scratches, cuts, abrasions, excessive hair, recent tattoos (within 6 months of study start) or other dermatological conditions on either upper arm that may affect the application of the study patch or the systemic absorption of fentanyl from the patch.

c. Procedures/Observations

i. Study Periods: two (2)

ii. Washout: There was a 14-day interval between dose applications.

iii. Administration and Removal of Patches

All patches were applied to the upper arm to an area where the site of application did not contain scratches, cuts, abrasions, excessive hair, recent tattoos (within 6 months of study start) or other dermatological conditions that may affect the application of the study patch or the systemic absorption of fentanyl from the patch.

Approximately one hour prior to application of the patches, the site was gently cleaned with warm water and allowed to air dry. No soaps or cleansing agents were used to clean the application site.

The patches were applied immediately after removal from its outer package taking care not cut or damage the patch prior to or during the application process. Application of the patch was performed by one of the study staff by pressing the patch firmly into place and holding it against the skin with the palm of the hand for approximately 30 seconds. In the second period of the study, the opposite arm was used for drug application.

The patches were removed 72 hours after initial application and any remaining gel was gently removed using warm water and allowed to air dry. No soaps or cleansing agents were used to clean the application site for at least 12 hours after the patch was removed.

Naltrexone was not administered during this study unless the severity or frequency of adverse events became intolerable.

Reviewer's comments: *Review of the sponsor's data indicates that no subject received naltrexone during this study.*

iv. Confinement & Meals

During the confinement periods of this study, the subjects were housed and fed at the clinical facility. Dosing in this study began on 7/23/04 and the study was completed on 8/12/04.

In each period, subjects reported for check-in. Subjects were released from the clinical facility approximately 144 hours after dosing in each study period.

d. Restrictions

i. Medications & other substances: Prior to each check-in for the study, the subjects were instructed to take no prescribed medications for at least 14 days (other than contraceptives) or over-the-counter medications for at least 3 days prior to the initial dosing and throughout the time of sample collection. No medications were permitted during the confinement except those administered. Subjects were also instructed to abstain from any products containing alcohol, grapefruit or caffeine/xanthine containing products for 24 hours prior to dosing and throughout the periods of blood collection. None of the subjects reported taking any restricted substance within the time frame indicated.
ii. Water: During the confinement periods of the study, water was encouraged *ad lib* at all times. Intake of fluids other than water and those provided with meals were not permitted.
iii. The use of tobacco was restricted for 30 minutes prior to any vital sign measurement.

iv. No strenuous physical exercise was permitted during confinement.
v. Application site: The subjects were required to avoid using soap or cleansing agents around or over the patch while it was in place and for 12 hours after removal. The subjects were also instructed to avoid allowing the site of application to become excessively wet during the study. If any of the patches were removed prior to the 72 hours application interval, the subject was dropped from the study.

Reviewer's comment: *The results indicate that only one patch fell off during the study. One test patch detached in period one, and the subject was discontinued from the study and never received the reference patch, so there is no test/ reference comparison for this subject.*

e. Safety

Urine pregnancy tests were performed on all female subjects at each check-in. Urine drug screens were performed at each check-in. Vital signs were measured before dosing and at regular intervals throughout both study periods. Subjects who sustained intolerable adverse events were to be administered oral naltrexone as appropriate for the relief of symptoms. Blood samples were collected from all subjects who completed the study at the end of Period II for clinical evaluations.

f. Removal of Subjects from Therapy or Assessment

i. Subjects were advised that they were free to withdraw from the study at any time for any reason.
ii. The Investigator or sponsor withdrew a subject from the study to protect the health of a subject.
iii. Subjects were also withdrawn for not complying with study procedures.

g. Endpoints

i. Pharmacokinetic Samples

In each period, blood samples were collected pre-dose and at intervals over 144 hours after initial patch application.

Reviewer's comment: *For the purpose of this review, only the adhesion data was evaluated. The pharmacokinetic data has been reviewed by the Division of Bioequivalence.*

ii. Irritation Evaluations

The application site was assessed at approximately thirty minutes and at approximately 24 hours after patch removal for skin irritation and was rated according to the Irritation Rating Scales below:

Irritation Scoring:

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible, minimal edema or minimal popular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Other Effects:

0	No other observations
1	Slight glazed appearance
2	Marked glazing appearance
3	Glazing with peeling and cracking
4	Glazing with fissure
5	Film of dried exudates covering all or part of the patch site
6	Small petechial erosions and/or scabs

Reviewer's comments: *Given that subjects received only one application of each test material (i.e., test and reference), irritation data collected during this study provides limited information.*

iii. Adhesion Evaluations

The application site was inspected at approximately 12, 24, 36, 48, 60 and 72 hours post-application for patch adhesiveness and was rated according to the Adhesiveness Rating Scale below. Throughout the duration of patch application, the patch site was observed to confirm adhesiveness of the study patch to the upper arm.

Adhesion Scoring:

0 =	≥90% adhered (essentially no lift off of the skin)
1 =	75% to <90% adhered (some edges only lifting off of the skin)
2 =	50% to <75% adhered (less than half of the system lifting off the skin)
3 =	<50% adhered, but not detached (more than half the system lifting off of the skin but not detached)
4 =	patch detached (patch completely off the skin)

h. Statistical analysis plan

i. Patient Population

Those patients who completed both periods of the study were included in each of the sponsor's analysis.

ii. Irritation

The irritation assessment means were calculated by the sponsor by adding together all the irritations scores for each treatment for those subjects who completed both periods of the study and dividing by the number of assessments.

iii. Adhesion

The adhesiveness assessments means were calculated by the sponsor by adding together all the adhesiveness scores for each treatment for those subjects who completed both periods of the study and dividing by the number of assessments.

iv. Safety

Not specified by the sponsor.

5. Study Conduct

a. Discussion of compliance
The sponsor reported that there were no protocol exceptions noted during this study.

b. Randomization/Blinding
Treatments were administered according to a randomization schedule prepared by Novum Pharmaceutical Research Services prior to the first dosing period.

c. Reserve Samples
Not provided by the sponsor.

Reviewer's comments: *The sponsor should refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, the sponsor should refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples should be randomly selected from each drug shipment by each study site prior to dispensing the medication to subjects. Samples must be randomly selected at each investigational site where the medication is dispensed and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time.*

d. Subject population (number included/excluded)
A total of 36 subjects were entered into this study and 31 subjects completed the study. The following subjects did not complete the study:

i. Subject 14 was withdrawn from the study due to a serious adverse event (SAE) experienced during the wash-out period of the study. (Please see "Comparative Review of Safety" for details.)

ii. Subject 16 was withdrawn from the study due to the patch coming off approximately 35 hours and 18 minutes post-application on 7/24/04.
iii. Subjects 21 and 23 were withdrawn from the study at Period II check-in on 8/5/04 due to a positive alcohol test.
iv. Subject 36 was withdrawn from the study at Period II check-in on 8/5/04 due to a positive urine pregnancy test. A second urine pregnancy test and a serum pregnancy test confirmed the initial results. The subject was referred to her own personal physician (OB/GYN) for follow-up. The subject reported that she visited her physician on 8/12/04 and subsequently terminated the pregnancy on (b) (6).

***Reviewer's comments**: The above subjects should be excluded from the PP population for the following test article:*

- *Treatment B (Test): Subjects 14 and 21*
- *Treatment C (Reference): Subjects 16, 23, and 36*

e. Patient Demographics (per sponsor)

Demographic Characteristics	
Gender	
Male	25 (69.4%)
Female	11 (30.6%)
Race/Ethnicity	
African American	20 (55.6%)
Caucasians	13 (36.1%)
Hispanics or Latinos	1 (2.7%)
Other	2 (5.6%)

	Age (years)	**Weight (lb.)**	**Height (in.)**
N	36	36	36
Mean	27.2	168.8	69.1
Median	23.5	166.5	69
SD	8.5	31.2	3.6
Range	18.0-39.0	125–248	79

6. Results

a. Irritation (per sponsor)
The sponsor reported that the mean irritation score of Test B was 1.19 and the mean irritation score for Reference C was 1.52. According to the sponsor's analysis, the test product appears to be lesson more irritating than the reference product in this study. Irritation scores for all subjects are provided in Table C6 in Section 3 of the sponsor's study report.

***Reviewer's comments:** Given that the subjects received only one application of each test material (i.e., test and reference), irritation data collected during this study provides*

limited information. Therefore, the FDA statistician was not requested to analyze the irritation data from this study.

b. Adhesion (per sponsor)

The sponsor reported that the mean adhesiveness score for Test B = 0.26 and the mean adhesiveness score for Reference C = 2.94. Both patches adhered well and only one test patch fell off during the study. However, there was no reference patch application for that subject, and no other test application had a score >1, while two reference applications had adhesion scores of 2 at 48 hours, five had adhesion scores of 2 at 60 hours, four had scores of 2 at 72 hours, and four had scores of 3 at 72 hours. According to the sponsor's analysis, the test product appears to have better adhesive properties than the reference product. Adhesiveness scores from all participants are provided in Table C7 in Section 3 of the sponsor's study report.

Reviewer's comments:

- *It should be noted that the Test B patch for Subject 16 fell off during Period I of the study. As a result, Subject 16 was withdrawn from the study and did not receive the Reference C patch.*
- *Tables C.1 and C.2 below summarizes the adhesion scores for the various time points by this reviewer.*
- *The FDA statistician was requested to analyze the adhesion data from this study. The FDA statisticians results are provided in Tables C.3 and C.4.*

Table C.1 - Frequency of the Test (T, N=34) and Reference (R, N=32) Patches for Various Adhesion Scores (0 - 4) at Various Measurement Times (12 - 72 Hour) (per reviewer)

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
0	34	25	34	25	33	23	32	20	31	14	28	9
1	0	8	0	8	0	10	1	11	2	14	5	16
2	0	0	0	0	0	0	0	2	0	5	0	4
3	0	0	0	0	0	0	0	0	0	0	0	4
4	0	0	0	0	1	0	1	0	1	0	1	0

Table C.2 - Frequency Expressed as Percentage of Total Number of Test (T, N=34) and Reference (R, N=32) Patches for Various Adhesion Scores (0 - 4) at Various Measurement Times (12 - 72 Hour) (per reviewer)

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
0	100	78.1	100	78.1	97.1	71.9	94.1	62.5	91.2	43.8	82.4	28.1
1	0	25.0	0.0	25.0	0.0	31.3	2.9	34.4	5.9	43.8	14.7	50.0
2	0	0.0	0.0	0.0	0.0	0.0	0.0	6.3	0.0	15.6	0.0	12.5
3	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.5
4	0	0.0	0.0	0.0	2.9	0.0	2.9	0.0	2.9	0.0	2.9	0.0

Table C.3 - Frequency distribution of adhesion score for the PP population* (per FDA Statistician)

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
62 paired scores												
0	31	28	31	24	31	22	30	19	29	13	26	8
1		3		7		9	1	10	2	13	5	15
2								2		5		4
3												4
67 available scores												
0	34	29	34	25	33	23	32	20	31	14	18	9
1		4		8		10	1	11	2	14	5	16
2								2		5		4
3												4
4					1		1[#]		1[#]		1[#]	

* T=test, R=reference

[#]: Test patch from subject 16 fell off at Hour 36. LOCF was applied at Hour 48, 60, and 72.

Table C.4 - Analysis of mean adhesion scores* using mixed model (per FDA Statistician)

Adhesion score	Test LS mean	Reference LS mean	95% Upper Confidence Bound (test-1.25 ref.)	Pass Non-inferiority Test?
62 paired scores	0.0430	0.4892	-0.3912	*Yes*
67 available scores	0.1161	0.5539	-0.4026	*Yes*

* Mean adhesion score per subject is equal to the sum of adhesion scores at Hour 12, 24, 36, 48, 60, and 72 per each subject and divided by 6.

D. Comparative Irritation Conclusion

In the 37-subject irritation study (770-0407-01), the data from the daily placebo TDS applications were compared to those of the daily applications of the negative control (0.9% sodium chloride) and the daily applications of the positive controls (0.02% and 0.04% SLS). The FDA statistical review confirmed that the study data showed the irritation potential of the placebo TDS to be worse than the negative control but no worse than that of the positive control. The non-inferiority test was passed for the daily placebo TDS versus the positive controls, therefore meeting the established criteria to support approval of the application. Comparison of the number of test vs. reference patches with irritation scores >/= 2 and >/= 3 support the results of the mean score analysis.

E. Comparative Skin Sensitization Conclusion

Using the conservative definition of a numeric dermal response score of ≥ 1 AND a letter response, none of the subjects in the sensitization study (770-0407-03) was considered potentially sensitized 48-hours and 72-hours post-removal of the challenge patch. Therefore, the potential of the placebo fentanyl TDS to induce sensitization is expected to be minimal, as is expected with use of the RLD.

F. Comparative Adhesion Conclusion

In the 36 subject pharmacokinetic study (770-0407-02), Teva's proposed Fentanyl TDS was compared to the RLD. The FDA statistical consultant confirmed that the mean adhesion scores from the pharmacokinetic study demonstrate non-inferiority of the proposed Fentanyl TDS compared to the RLD. Comparison of the proportion of test vs.

reference applications with scores greater than 1 and scores greater than 2 support the conclusion of the mean score analysis.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

Given that the placebo studies did not compare the proposed test product to the Reference Listed Drug, the adverse events reported during these studies reflect only the local skin effects of the inactive ingredients. The local adverse events reported during these studies appear to be minor and would not preclude the approval of this application.

B. Description of Adverse Events

"A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Healthy Adult Subjects" (Protocol 770-0407-01)

According to the sponsor, nine adverse events (AE) were reported by 9 of 37 subjects. All AEs were mild to moderate in severity and no serious adverse events were reported. A total of nine AEs were experienced post-treatment by the subjects who completed the study. Of the nine reported AEs, one (Burning on site D) was related to the test article. In the opinion of the clinical investigators, the remaining eight (sprained ankle, back pain, sore throat x 2, torn toe nail, vomiting, headache and frequent urination/burning while urinating) were unrelated to the test articles.

"Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects" (Protocol 770-0407-03)

During the study, AEs were mild or moderate in severity and no serious adverse events were reported. A total of 129 AEs were experienced post-treatment by the subjects. In the opinion of the clinical investigators, the 129 AEs were unrelated to the test articles. None of the AEs were considered serious.

"A Study to Evaluate the Relative Bioavailability of a Fentanyl Patch Transdermal Delivery System (25 mcg/hr) Compared to Duragesic® (Fentanyl Transdermal System) 25 mcg/hr Patches" (Protocol 770-0407-02)

Table D.1 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Nausea	16	17
Erythema (1, minimal)*	19	9
Erythema (2, definite)	3	12
Euphoric	0	1
Emesis	13	10
Itchy, generalized	11	10
Light headed	1	5
Pain in the body	1	3
Headache	7	6
Tingling sensation	1	0
Insect bites, bilateral lower extremities	1	0
Tired	2	3
Upset stomach	1	2
Dizzy	3	3
Abdominal cramping	3	0
Popping sound both ears	0	1
Difficulty sleeping	0	1
Elevated blood pressure	4	3
Decreased blood pressure	0	4
Tender, right lateral forearm	0	1
Edema	0	1
Ecchymosis	0	1
Elevated temperature	1	1
Purulence	0	1
Elevated WBC	0	1
Elevated sedimentation rate	0	1
Elevated C-reactive	0	1
Sleepy	3	1
Woozy	1	0
Papules (3)	1	1
Erythema (3)	1	1
Abnormal sensation	0	1
Feeling high	3	3
Hot flash	0	1
Hot	2	0
Numbness	0	1
Anxious	1	0
flushed	1	0
sleepless	0	1
Papules (2)	0	1
Total:	**100**	**110**

* irritation score

The subjects were monitored throughout the study for any adverse experiences. They were encouraged to report signs, symptoms, and any changes in health to study personnel. None of the adverse events experienced by the subjects during this study were judged as serious with one exception. Subject 14 experienced adverse events of "tender, swollen, bruised area of the right lateral forearm" that was the result of bumping his arm on the sink during Period I confinement. The subject completed the study period and was released on 7/29/04. Prior to leaving the facility he was seen by a medical Investigator and found stable for release. On 7/31/04 the subject's arm worsened and the subject was seen in a local emergency room where he was administered intravenous and oral antibiotics. On (b) (6), the symptoms continued. The subject returned to the hospital where he was admitted and treated with intravenous antibiotics. His symptoms still did not improve and the area was irrigated and debrided (I&D) surgically. On (b) (6) the subject was again taken to the operating room for I&D and packing of the wound. The subject notified the clinic staff on (b) (6). The subject was then withdrawn from the study, medical records were requested and the Sponsor and NIIRB were informed on (b) (6). The subject returned to Novum on 10/6/04 for his post-study evaluations and his right arm wound was assessed and considered to be resolved.

VI. Relevant Findings From the Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Division of Scientific Investigations

A request for investigation was submitted on August 8, 2005. DSI conducted two clinical site inspections (EIR review dated September 7, 2006). One site (Fargo, ND) has been classified as NAI (no Action Indicated). The second site (San Diego, CA) has been classified as VAI (Voluntary Action Indicated). During the inspections, DSI issued FDA Form 483.

The objectionable findings (pertaining to the conduct of protocol 770-0407-01) were as follows:

> The protocol was not followed in that subjects 332 and 333 did not receive all required patches throughout the study. Deviation reports in case histories and the Study Report indicate that the positive and negative control patches were dropped on 7/28/04 and 7/27/04, respectively, due to tape irritation. The subjects were not discontinued from the study and their respective irritation scores were reported for all time points and patches in the Study Report dated 9/14/04.

DSI reported that the residual irritation scores were included in the final statistical analyses.

Reviewer's Comments:

- *Regarding the objectionable finding from the DSI inspection, the worst case in including subjects 332 and 333 in the analyses is that the positive control looks less irritating, which should not adversely impact approval decision.*
- *Given that DSI categorized this deficiency as VAI (voluntary action indicated),the remainder of the data from this study need not be discarded due to this deficiency.*

B. Statistics

1. Irritation Analysis

The mean total irritation score from the irritation study (770-0407-01) was analyzed using the mixed model as shown below:

Analysis result for mean total irritation score using the mixed model Test placebo versus Negative and Positive controls

Comparator	LS mean (A: Test placebo)	LS mean (Comparator)	Upper limit one-sided 95% CB (T-1.25 B)	Pass the Non-Inferiority Test?
Negative control	0.6759	0.1772	0.5722	No
Positive control (0.02%)	0.6759	0.6799	-0.05406	Pass
Positive control (0.04%)	0.6759	2.0384	-1.7057	Pass

Reviewer's Comment: *Based on the FDA statistical analysis, the data in this study demonstrated non-inferiority of the placebo fentanyl patch compared to a mild irritant control regarding irritation potential.*

2. Sensitization Analysis

No subject was identified by the FDA statistician as potentially sensitized:

Frequency distribution of sensitization score at Hour 48 and 72 in the challenge period

Hour	Patch	Score		Total
		0	0P	
48*	Test placebo patch	172	6 (63, 71, 147, 186, 207, 209)	178
	Negative control patch	175	3 (68, 77, 103)	178
72	Test placebo patch	178	1 (207)	179
	Negative control patch	179		179

*: Subject 117 missed visit at Hour 48

Reviewer's Comment: *Using the conservative definition of a numeric score of ≥ 1 AND a letter response persisting to the 48 and/or 72 hours post patch removal during the challenge period no subject was considered potentially sensitized. Therefore, the potential of the placebo fentanyl TDS to induce sensitization is expected to be minimal, as is expected with use of the RLD.*

3. Adhesion Analysis

The mean adhesion score from the pharmacokinetic study (770-0407-02) was analyzed using a mixed model as shown below:

Analysis of mean adhesion scores* using mixed model

Adhesion score	Test LS mean	Reference LS mean	95% Upper Confidence Bound (test-1.25 ref.)	Pass Non-inferiority Test?
62 paired scores	0.0430	0.4892	-0.3912	*Yes*
67 available scores	0.1161	0.5539	-0.4026	*Yes*

* Mean adhesion score per subject is equal to the sum of adhesion scores at Hour 12, 24, 36, 48, 60, and 72 per each subject and divided by 6.

Reviewer's Comment: *Based on the FDA statistical analysis, the data in this study demonstrated non-inferiority of the fentanyl patch compared to the RLD regarding adhesion performance.*

VII. Formulation

Reference Listed Drug - Duragesic®

Component	**System size (cm^2)**			
	25 mcg/hr	**50 mcg/hr**	**75 mcg/hr**	**100 mcg/hr**
Occlusive Backing Film, Polyester/EVA				(b) (4)
Drug Reservoir Fentanyl Base Hydroxyethyl Cellulose, NF (b) (4) Ethanol, 95%, USP	2.5	5	7.5	10 (b) (4)
Release Membrane Film, EVA (b) (4)				
Contact Adhesive Silicone Adhesive (b) (4)				
Protective Liner (b) (4)				
Total Weight	**659**	**1255**	**1810**	**2377**

Fentanyl Transdermal System (proposed generic)

Component	Basis Weight mg/cm^2	% WW	10.7 cm^2 (25 mcg/h)	21.4 cm^2 (50 mcg/h)	32.1 cm^2 (75 mcg/h)	42.8 cm^2 (100 mcg/h)
[redacted]						

(b) (4)

Reviewer's Comments:

- *Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) was consulted for a pharmacology toxicology review of the safety assessments for* ***polyisobutene/polyisbutylene*** *adhesives and* [redacted] (b) (4) *and tolerance and toxicology studies for* [redacted] (b) (4)*. In the December 16, 2005 consult response, the reviewer concluded that the safety assessment completed by the Sponsor's toxicology consultant are not adequate for a dermal application and that the submitted toxicology studies are not supportive of the materials present in the drug product. However, the reviewer also noted that the materials in question may already be used in approved products (i.e., Nicotrol Nicotine Transdermal System, Ortho Evra Transdermal System and Vivelle). Subsequently,* [redacted] (b) (4) *and* [redacted] (b) (4)*, on behalf of TEVA Pharmaceuticals, submitted additional toxicology data. A second pharmacology toxicology consult request to DAARP was submitted regarding the safety of* [redacted] (b) (4) [redacted] (b) (4)*. In the July 23, 2007 consult response, the reviewer concluded that there does not appear to be significant safety concerns with the use of* [redacted] (b) (4) *polymers).*
- *The amount of fentanyl per patch is about 10.42% greater than in the RLD with a similar patch surface area.*

Previous ANDAs for this product have been approved with a 10% greater total fentanyl content. (b) (4) *reater amount of fentanyl than the RLD. Likewise, the fentanyl transdermal application* (b) (4) *The approved application by Lavipharm (77-051) and the pending ANDA 77-154 by Tyco Healthcare Mallinckrodt's both have a matrix system containing 10% more fentanyl than the RLD, similar to this Teva product containing10.4*(b) (4)*% more fentanyl than the RLD. Please see Table D.1 for comparative content of the products.*

Table D.1 - Drug content and drug delivery area for different ANDAs

Dose (µg/h)	Test product (Teva, 77449)		Reference product		Test product (Mylan, 76258)	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	10.7	2.76 (b) (4)	10	2.5	6.25	2.55
50	21.4	5.52	20	5	12.5	5.1
75	32.1	8.28	30	7.5	18.75	7.65
100	42.8	11.04	40	10	25	10.2

Dose (µg/h)	Test product (b) (4)		Test product (Watson, 76709)		Test product (b) (4)	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	(b) (4)		10	2.5	(b) (4)	
50			20	5		
75			30	7.5		
100			40	10		

Dose (µg/h)	Test product (Lavipharm, 77051)		Test product (Abrika, 77062)		Test product (Tyco, 77154)	
	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.75	10	2.5	7.8	2.75
50	20	5.5	20	5	15.6	5.5
75	30	8.25	30	7.5	23.4	8.25
100	40	11.0	40	10	31.2	11.0

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 77-449 demonstrate that the skin irritation potential of Teva Pharmaceuticals USA's placebo Fentanyl Transdermal System, 25 mcg/hr is no worse than that of the positive controls (0.02% and 0.04% sodium lauryl sulfate) of low irritancy, and the potential of Teva's placebo fentanyl TDS to induce sensitization is minimal, as expected with use of the RLD. The data also demonstrate that the adhesive performance of the Teva fentanyl TDS is at least as good as that of the RLD.

B. Recommendation

The Clinical Review Team recommends that the skin irritation, sensitization and adhesion data submitted to ANDA 77-449 are adequate to support approval of the application.

_____ _____

Sarah H. Seung, Pharm.D. Date
Clinical Reviewer
Office of Generic Drugs

_____ _____

Dena R. Hixon, M.D. Date
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____

Barbara M. Davit, Ph.D., J.D. Date
Acting Director
Division of Bioequivalence II
Office of Generic Drugs

CLINICAL REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:77-449 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 77-449 are adequate to demonstrate that the irritation potential of Teva Pharmaceuticals USA's (Teva) placebo Fentanyl Transdermal System (TDS), 25 mcg/hr is no worse than that of positive controls (0.02% and 0.04% sodium lauryl sulfate) of low irritancy.

The data also demonstrate minimal potential of Teva's placebo Fentanyl TDS to induce sensitization, as expected with use of the RLD, Duragesic®.

The data also demonstrate that the adhesive performance of Teva's Fentanyl TDS is at least as good as that of the RLD.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dena Hixon
9/22/2008 01:01:23 PM
MEDICAL OFFICER
Signed for Sarah Seung, primary author. As team leader, I concur with this review.

Barbara Davit
9/22/2008 04:45:20 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

STATISTICAL REVIEWS

ANDA 77-449
Drug Product: Fentanyl Transdermal System, 25/50/75/100 mcg/hr
Sponsor: Teva Pharmaceuticals USA
Submission date: 12/17/2004

Reviewer: Huaixiang Li, Ph.D., DIV6/OB/CDER
Requestor: Sarah Seung, Pharm.D., OGD/CDER, 8/7/07

Contents of Review

SAS datasets

This statistical review used the SAS datasets and programs submitted to the Electronic Document Room (EDR), CDER for an irritation study (protocol 770-0407-01), a sensitization study (protocol 770-0407-03), and a PK-adhesion study (protocol 770-0407-02) on January 31, 2007.

Introduction

Fentanyl is an opioid analgesic indicated for the management of chronic pain in patients who require continuous opioid analgesia for pain. Teva Fentanyl placebo patch (test placebo patch) has all of the same inactive ingredients and is identical to the sponsor's proposed product in every manner except for the absence of fentanyl.

This review refers to a PK-Adhesion study (protocol 770-0407-02) to compare adhesion of Teva Fentanyl Transdermal System versus the reference listed drug (RLD), Alza's Duragesic® - active patches; an irritation study (protocol 770-0407-01) for assessment of irritation for Teva Fentanyl placebo patch versus the comparators (positive/negative control patches); and a sensitization study (770-0407-03) to evaluate the incidence of allergic contact dermatitis following repetitive applications of Teva Fentanyl placebo patch versus negative control patch.

Outcome variables

The following scales were used by the sponsor for irritation, sensitization, and adhesion evaluation:

Skin Irritation Scoring Scale*

Skin irritation response - numeric grades	Skin irritation response - letter grades
0 = No evidence of irritation 1 = Minimal erythema, barely perceptible 2 = Definite erythema, readily visible; minimal edema or minimal papular response 3 = Erythema and papules 4 = Definite edema 5 = Erythema, edema and papules 6 = Vesicular eruption 7 = Strong reaction spreading beyond test site	A = slight glazed appearance B = marked glazed C = glazing with peeling and cracking F = glazing with fissures G = film of dried exudate covering all or part of the patch site H = small petechial erosions and/or scabs

*: The total irritation scoring scale was used for statistical analysis in the irritation study. Irritation letter grades were converted to numerical equivalents as follows: 1:2:3:4:4:4 for letter A:B:C:F:G:H for our (OGD/FDA) statistical analysis. These numerical equivalents were considered additive to the numerical grades (e.g., 2H = 2 + 4 = 6).

Skin Sensitization scoring Scale*

Skin sensitization response - numeric grades	Skin sensitization response - letter grades	Skin sensitization response - additional observation grades
0 = No visible reaction or erythema 1 = Mild reaction, macular erythema (faint, but definite pink) 2 = Moderate reaction, macular erythema (definite redness, sunburn appearance) 3 = Strong to severe reaction, macular erythema (intense redness)	E = Edema (swelling, spongy feeling when palpated) P = Papule (red, solid, pinpoint elevations, granular feeling, <5 mm diameter) V= Vesicles (fluid-filled lesion <5 mm diameter) B= Bulla (fluid-filled lesion >5 mm diameter) S= Spreading (evidence of the reaction beyond the patch area) W= Weeping (serous exudates, clear fluid oozing or covering patch site) I= Induration (solid, elevated, hardened, thickening skin reaction)	g = Glazing p = Peeling c = Scab, dried film of serous exudates d = Hyperpigmentation, reddish-brown discoloration h = Hypopigmentation, loss of visible pigmentation f = Fissuring, grooves in the superficial layers of the skin

*: The sensitization scoring scale was used in the induction and in the challenge phases of the sensitization study. The letter grades were not converted to numerical value in the induction phase. "A sensitization numeric score ≥ 2" or "A numeric grade ≥ 1 AND the presence of a letter grade (E, P, … etc.)" were considered a sensitized score for our (OGD/FDA) sensitization analysis.

Symbols Used in Tabulating Data and/or Deviations

O	Original application site
M	Adjacent site (application following strong reaction during induction)
M-1	Second adjacent site
A	Naïve adjacent site used during challenge application
X	Patch omitted due to previous strong reaction
XR	Patch omitted for reasons unrelated to the test material
L	Test patch worn less than 23 hours
--	Subject absent
DR	Subject dropped from study
(C)	Comments included below or on supplemental information page

These symbols, 'X', 'XR', 'L', '--', and 'DR' were converted to missing values in the analysis.

Adhesion scoring

0 =	≥90% adhered (essentially no lift off of the skin)
1 =	75% to <90% adhered (some edges only lifting off of the skin)
2 =	50% to <75% adhered (less than half of the system lifting off the skin)
3 =	<50% adhered, but not detached (more than half the system lifting off of the skin but not detached)
4 =	patch detached (patch completely off the skin)*

*: When an adhesion score reached 4, this score was carried forward to the last evaluation time, Hour 72.

Remark according to the OGD medical reviewer's comments

Clinical endpoint definitions

Mean adhesion score for the adhesion study: The mean adhesion score per each subject is obtained by adding skin adhesion scores at each evaluation time (Hour 12, 24, 36, 48, 60, and 72), and dividing by the number of scores (e.g., 6).

Mean total irritation score for the irritation study: The total irritation score is equal to the skin irritation numeric score plus the score converted from the irritation letter response per each visit day per each subject. The mean total irritation score per each subject is obtained by adding total irritation scores for each evaluation visit, and dividing by the number of scores.

Sensitized score in the challenge phase of the sensitization study: "A sensitization numeric score ≥ 2" or "A sensitization numeric score ≥ 1 AND a letter response (e.g., 1E)" was defined as a sensitized score. A subject who had a sensitized score at Hour 48 and/or 72 was considered potentially sensitized. However, if the sensitized score was present at Hour 48, but cleared at Hour 72, this subject should not be considered potentially sensitized.

Since the addition of the active drug could change the adhesive performance of the patch, only adhesion scores obtained from the PK-adhesion study were analyzed due to the fact that the subject wore active test and reference patches for 72 hours. In the irritation and sensitization studies, the patches were test placebo and negative/positive control (not active patch) which were worn for less than 72 hours, and so did not provide an adequate test of adhesion.

Total irritation score in the irritation study

When an intolerable irritation reaction happened (dermal response grade ≥3 or a surface score of grade F, G, or H), those patches causing excessive irritation were discontinued.

Last observation carried forward (LOCF): If the patch was discontinued/moved due to an intolerable irritation reaction, the last total irritation score (at the stopping/moving day) would be carried forward for statistical analysis.

The total irritation scores with LOCF were used for the frequency tables and statistical analysis for the Per-protocol (PP) population in the irritation study.

Statistical Analysis Methods

Sponsor's analysis for irritation scores

The sponsor converted irritation letter grades to numerical equivalents as follows: 0:1:2:3:3:3 for letter A:B:C:F:G:H. These numerical equivalents were considered additive to the numerical grades. An upper limit of 3 for total score was selected.

The overall total score for each test article was ranked within each subject and then analyzed using the Friedman rank sum test. The hypotheses for this test were as follows:

H_0: The rank sums of the test articles are identical.

H_a: At least two of the rank sums differ.

The Fishers LSD test 8[1] was performed if significant differences ($p < 0.05$) were observed within the Friedman rank sum test.

The sponsor also provided the analysis result for irritation scores based on the method recommended by Berger, R.S., Bowman, J.P. *(1982). A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol. Cut. & Ocular Toxicol. 1(2), 109-115*. The cumulative/sum total irritation scores per each patch treatment for base =10 (i.e. a theoretical standardized study of ten subjects) were derived by applications of the equations below:

Total score (TS) = $\sum_{i=1}^{21}\sum_{j=1}^{N} S_{ij}$

Total score for 10 subjects (TS10) = (10)(1/N)(TS)

Where S_{ij}, for each treatment, is the total irritation score for the i^{th} day for the j^{th} subject and N is the total number of subjects. Any S_{ij} score > 3 is replaced by a 3, and if a patch treatment is discontinued because of a high irritation score, scores of 3 are carried forward for the remainder of the 21 days. The possible range of TS10 is 0 to 630.

The variable TS10 is categorized as 0-49:50-199:200-449:450-580:581-630 into class 1:2:3:4:5 for 21 evaluations. Please see the detailed explanation on page 17-19 in the OGD medical reviewer's report. Interpretation of the different irritation classes is provided on page 16-18, section VI.7.b of the sponsor's report.

There are three difficulties with this method: 1) Possible correlations of the irritation scores per each patch taken from the same subject couldn't be accommodated. 2) The method provides no upper confidence bound for carrying out the non-inferiority test. 3) The upper limit total irritation score was limited to 3 (e.g., 2C=2+3=5 was limited to 3). Such truncation of the score could possibly decrease any average differences between articles.

[1] It is almost certainly a typographical error here. Analysis method "Fisher's LSD 8" was a page of the index to a book titled "Practical Data Analysis for Designed Experiments" by Brian S Yandell. The index is actually to "Fisher's LSD", but the first reference page is page 8. Perhaps someone read this wrong and dutifully wrote it out as "Fisher's LSD 8".

FDA's analysis for irritation scores and adhesion scores

In the irritation study, each subject used all of four articles: daily application (21 applications in 21 days) for the test placebo, the negative control, and two positive controls (0.02% and 0.04% Sodium Lauryl Sulfate) patches. In the sensitization study, each subject used the test placebo and negative control patches for 3 applications per week in the induction phase (9 applications in three weeks) and one application in the challenge phase. In the adhesion study, each subject used both test and reference active patches. Consequently, the irritation scores, sensitization scores, and adhesion scores per each patch taken from the same subject might be correlated. The statistical analysis method should reflect these correlations.

Mixed model

The random effects in the mixed model (used for analysis of irritation and adhesion scores) structure assessed and reflected the correlation of the measurements. The analysis was carried out using the Proc Mixed procedure in SAS® (version 9.1), with treatment as a fixed effect and subject as a random effect in the model.

The test statistics used the estimated *adjusted mean difference* μ_1-1.25μ_2, which was based on the hypothesis

$$H_0: \mu_1 - 1.25\mu_2 > 0 \qquad \text{vs} \qquad H_1: \mu_1 - 1.25\mu_2 \leq 0$$

where μ_1 is the mean response for the test product and μ_2 is the mean response for the comparator. One-sided 95% upper confidence bounds (CBs) were obtained based on the estimates of μ_1-1.25μ_2. If this upper limit was less than or equal to 0, the null hypothesis was rejected and the test product could be considered Non-inferior to the comparator. Otherwise, it was concluded that the test product may be worse than the comparator.

The mixed model analyses were carried out using the following program statements in SAS (version 9.1):

```
proc mixed data=<dataset name>;
 class subject trt;
 model X = trt/ddfm=satterth;
 repeated trt/sub=subject type=fa0(2) r;
 lsmeans trt;
estimate 'a-1.25b' int -0.25 trt 1 -1.25/cl alpha=0.1;
run;
```

The PK adhesion study was conducted as a two-treatment, two-period crossover design. We analyzed the study with a crossover analysis, but found no evidence of period or sequence effects ($p \geq 0.3886$ for period, $p \geq 0.2460$ for sequence.) For this reason, the mixed model described above was used to analyze the PK adhesion study as well as the irritation study.

Analysis of sensitization rates

McNemar confidence bound

For sensitization analysis, the sensitization scores were dichotomized to sensitized and non-sensitized. The analysis then seeks to compare the sensitization rates between the Test product and the comparator product. McNemar published an important paper (McNemar, Q. (1947), Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*. 12(2):153-157) on inference concerning proportions estimated from correlated samples. The McNemar test is a frequently used method for analyzing the data from matched samples with a dichotomous outcome when the objective is to test the hypothesis H_0: $p_T = p_R$. Fleiss published a formula (page 117 of *Statistical Methods for Rates and Proportions* (second edition, John Wiley and Sons, 1981) by Joseph L. Fleiss) for confidence bounds for the difference between proportions in the matched pairs context, using results presented in McNemar's 1947 paper.

To assess the Non-Inferiority of the Test product to the Reference Product, a 95% upper confidence bound (CB) for the difference between the proportions p_T and p_R was calculated, where
p_T = Population sensitization rate of the Test product, p_R = Population sensitization rate of the Reference product.

Further,
n = number of subjects, b = number of subjects sensitized to the Test product but not to the Reference product, and c = number of subjects sensitized to the Reference product but not to the Test product.

The hypothesis to be tested was,

H_0: $p_T - p_R > \delta$ vs. H_1: $p_T - p_R \leq \delta$

where δ is a given non-inferiority bound.

The difference $p_T - p_R$ may be estimated by the quantity $(b - c)/n$.
A 95% upper confidence bound (CB) for the quantity $p_T - p_R$ was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645 \frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given on page 117 of Fleiss (1981).

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity $p_T - p_R$ is less than or equal to δ, that is: $U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the Test product to the Reference product.

Study 770-0407-02 (PK study used for adhesion analysis)

A Randomized, Single Dose, Two-Way Crossover, Evaluation Designed to Compare the Absorption of Fentanyl From Teva's Patch Product and a Reference Patch, Duragesic®, in Healthy Subjects. All subjects received both active patch applications for 72 hours at the same spot on separate sites. The study had two periods: half of the subjects applied the active test patch and the others applied the active reference patch in Period 1. After a 14-day washout period, the subjects switched the patch application (test to reference or reference to test) in Period 2. The assignment of the test articles to the test sites was randomized. Patch adhesion was evaluated at 12, 24, 36, 48, 60, and 72 hours post-dose by a trained observer.

36 subjects were randomized and provided total 67 available mean adhesion scores (34 from the test patch and 33 from the reference patch). 31 subjects completed the study and had 62 paired mean adhesion scores[2].

5 subjects were withdrawn from the study after Period 1. The subject number, the patch used in Period 1, and the reasons for withdrawal were: subject 14 (reference) - serious adverse event, subject 16 (test) - patch coming off, subjects 21 (reference) and 23 (test) - positive alcohol test, and subject 36 (test) - positive urine pregnancy test. These 5 subjects didn't apply any patch in Period 2.

Table 1.1 - Adhesion scores from 5 subjects in Period 1

Subject	Treat	Hour 12	Hour 24	Hour 36	Hour 48	Hour 60	Hour 72
14	Reference		(b) (4)				
16	Test						
21	Reference						
23	Test						
36	Test						

Table 1.2 - Frequency distribution of adhesion score*

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
62 paired scores												
0	31	28	31	24	31	22	30	19	29	13	26	8
1		3		7		9	1	10	2	13	5	15
2								2		5		4
3												4
67 available scores												
0	34	29	34	25	33	23	32	20	31	14	28	9
1		4		8		10	1	11	2	14	5	16
2								2		5		4
3												4
4					1		1#		1#		1#	

*: T=test, R=reference.
#: Test patch from subject 16 fell off at Hour 36. LOCF was applied at Hour 48, 60, and 72.

[2] Demographic information (gender, race, and age) couldn't be found in the electronic dataset.

Table 1.3 - Analysis of mean adhesion scores* using mixed model

Adhesion score	Test LS mean	Reference LS mean	95% Upper Confidence Bound (test-1.25 ref.)	Pass Non-inferiority Test?
62 paired scores	0.0430	0.4892	-0.3912	Yes
67 available scores	0.1161	0.5539	-0.4026	Yes

*: Mean adhesion score per subject is equal to the sum of the adhesion score at Hour 12, 24, 36, 48, 60, and 72 per each subject and divided by 6.

The mean adhesion score was analyzed using a mixed model and passed the Non-inferiority test for the 62 paired scores and 67 available scores.

Study 770-0407-01 (Irritation study)

This was a randomized, single-center, within-subject study design comparing skin irritation properties of the Test placebo patch, Negative control and Positive control patches, worn continuously at the same site and changed daily per each treatment patch in 21 days.

A. Test placebo patch (Placebo Fentanyl Transdermal System)
B. Negative irritant control, saline (0.9% - sodium chloride)
C. Positive irritant control, Sodium Lauryl Sulfate (0.02%, anionic surfactant)
D. Positive irritant control, Sodium Lauryl Sulfate (0.04%, anionic surfactant)

37 subjects received 21 consecutive daily (24±1 hour) patch applications of article A, B, C, and D to four separate test sites. To eliminate any position bias, the position of each article was randomly assigned to the skin site.

Of the 37 subjects enrolled into the study, 5 were male and 32 were female subjects. There were 27 Caucasians and 10 others. The mean age was 38 years and ranged from 18 to 62 years old.

Subject 337 was excluded from the sponsor's Per-Protocol population, this subject discontinued early from the study and did not have any irritation score in the dataset[3]. 36 subjects were included in the Per-protocol (PP) population.

No subject was discontinued due to intolerable irritation in the study. The highest irritation responses were 2C (total score: 2+3=5).

Frequency tables

Table 2.1 - Frequency of individual total irritation scores per each patch *per observation*

	Total score						Total number of scores
	0	1	2	3	4	5	
Test placebo	285	431	40				756 (36×21)
Negative control	628	122	6				756 (36×21)
Positive control (0.02%)	283	440	29	2		2	756 (36×21)
Positive control (0.04%)	85	177	168	298	6	22	756 (36×21)

[3] Subject 337 failed to return after visit 6 and did not give any reason.

Table 2.2 - Frequency of maximum total irritation scores per each patch *per subject*

	Maximum total score					Total number of subject
	0	1	2	3	5	
Test placebo	3	27	6			36
Negative control	16	17	3			36
Positive control (0.02%)		27	8		1	36
Positive control (0.04%)		1	1	24	10	36

Mixed model

Table 2.3 - Analysis results for mean total irritation score using the mixed model
Test placebo versus Negative and Positive controls (0.02% and 0.04%)

Conparator	Lsmean (A: Test placebo)	Lsmean (Comparator)	Upper limit one-sided 95% CB (T – 1.25 B)	Pass the Non-Inferiority Test?
Negative control	0.6759	0.1772	*0.5722*	*No*
Positive control (0.02%)	0.6759	0.6799	-0.05406	Pass
Positive control (0.04%)	0.6759	2.0384	-1.7057	Pass

As can be seen from the above table, the one-sided 95% upper CB for the adjusted mean difference ($\mu_A - 1.25\ \mu_{Comp}$) from the mixed model was positive for test placebo versus negative control, but negative for test placebo versus positive controls (0.02% and 0.04%). The non-inferiority test was failed for test placebo versus negative control, but passed for test placebo versus positive controls (0.02% and 0.04%).

Study 770-0407-03 (Sensitization study)

A single-center, randomized, single-blinded study of Teva's Placebo Fentanyl Transdermal System vs. a Negative (Saline) Control for evaluation of skin irritation and sensitization. The assignment of the test articles to the test sites was randomized and the skin reaction evaluator was blinded to the randomization of each subject and their previous scores.

Subjects received one test placebo (A) and one negative control (B) on two separate test sites. The patch application was scheduled on study days 1, 3, 5, 8, 10, 12, 15, 17, and 19 on two separate test sites in the induction period and the irritation score was evaluated using the sensitization scoring scale. All subjects who completed the induction period were scheduled to complete a rest period of 14-17 days without patch application. Then the patches were applied to naïve sites for 48 (±2) hours to observe the reactions indicative of contact sensitization in the challenge period. The sites were scored approximately 0.5, 24±1, 48±2, and 72±2 hours after patch removal using the sensitization scoring scale.

According to the sponsor's report, 220 subjects enrolled into the study. However, there were 216 subjects in the summary dataset (sum.xpt) and 217 subjects in the per-visit dataset (sen.xpt) submitted by the sponsor. Subject 95 wasn't included in the summary dataset and had only baseline visit in the per-visit dataset.

Of the 216 subjects included in the summary dataset, 45 were male and 171 were female. There were 202 Caucasians and 14 Others. The mean age was 33 years and ranged from 18 to 65 years old.

Exclusion from the FDA per-protocol (FPP) population[4]

- 12 subjects were already excluded from the sponsor's PP population. 7 subjects (75, 90, 95, 169, 178, 195, and 213) who dropped during induction phase and 5 subjects (65, 114, 116, 142, and 177) who dropped during challenge phase.
- 7 subjects, 004, 006, 026, 074, 133, 210, and 214, violated the protocol due to various reasons.
- 19 subjects, 8, 10, 14, 19, 28, 30, 44, 89, 94, 106, 124, 126, 127, 148, 154, 158, 200, 208, and 220, had patches that fell off during the challenge phase.

179 subjects were included in the FDA's per-protocol (FPP) population and were used for sensitization analyses in this review.

Table 3.1 - Frequency distribution of sensitization scores at Hour 48 and 72 in the challenge period

Hour		0	0P	Total
48*	Test placebo patch	172	6 (63, 71, 147, 186, 207, 209)	178
	Negative control patch	175	3 (68, 77, 103)	178
72	Test placebo patch	178	1 (207)	179
	Negative control patch	179		179

*: Subject 117 missed visit at Hour 48.

[4] Please see the details in the medical review report.

According to the OGD medical reviewer's comments, a sensitization score ≥ 2 or a sensitization score ≥ 1 AND a *letter response* (e.g. 1P) was defined as a sensitized score. No subject had a sensitized score from the test placebo patch or negative control patch at Hour 48 and 72 in the challenge phase of this study.

Table 3.2 –Two upper limit one-sided 95% confidence bounds (CB) for p_T - p_R

Hour	Number of Subjects	McNemar (%)	FDA (%)
48	178	0.5618	2.4788
72	179	0.5587	2.4652

Based on the 95% upper confidence bound (using the McNemar confidence bound as given by Fleiss) for the difference in sensitization rates, the Test patch rate may exceed the Reference patch rate by at most 0.5618/0.5587 percentage points at Hour 48/72.

Because the number of sensitized subjects was so small, there may be concerns about the accuracy of the confidence bound formula given by Fleiss. Using an alternate confidence bound method we have developed, which our research shows performs better than Fleiss's formula when probabilities are small, a 95% upper confidence bound for $p_T - p_R$ is 2.4788/2.4652 percentage points at Hour 48/72. These results help to establish the order of magnitude of the possible range of p_T - p_R. If the Non-inferiority limit were established as low as 3%, the Test product has been shown to be Non-inferior to the negative control.

Comments on the sponsor's analysis

Adhesion Study: The sponsor submitted the frequency tables for the adhesion scores for 67 available adhesion scores (34 from the test patch and 33 from the reference patch). The sponsor reported that the adhesion score (total) means were 0.26 for the test patch and 2.94 for the reference patch.

Irritation study: Statistically significant differences among test articles were observed with the Friedman rank sum test ($p < .0001$). The Fishers LSD Test determined that there were statistically significant differences among the Placebo, the negative control and the high (0.04%) positive control ($p < 0.01$). However, there was no statistically significant difference between the Placebo and the low (0.02%) positive control ($p > .05$).

The sponsor also provided the analysis result for irritation scores based on the method recommended by Berger, R.S., Bowman, J.P. *(1982).* The base 10 scores (class) were 140.83 (2) for the test placebo, 37.22 (1) for the negative control, 140.83 (2) for the positive control (0.02%), and 330.83 (3) for the positive control (0.04%). Their analysis methods were not used in our analysis.

Sensitization study: According to the sponsor's report, six subjects had a score of "0P" at the 48 hour challenge evaluation and one subject had a score of "0P" at the 72 hour challenge evaluation. These reactions are not indicative of allergic contact dermatitis.

Differences between Sponsor's Results and Our Results
Where the sponsor's results differ numerically from our own results, it is due to

1. Differences in the sponsor's PP population and our PP population (FPP.)
2. Different statistical analysis methods.
3. Differences between the sponsor and ourselves in the conversion of letter scores into numerical equivalents.

Summary and discussion

Study 770-0407-02 (PK-Adhesion study)
The mean adhesion score was analyzed using a mixed model and the Non-inferiority test was passed for test (Teva) versus reference (Alza's Duragesic®) active patches (see Table 1.3). Thus, based on these data, the non-inferiority test passed, and we can conclude that the mean in the population for the mean adhesion score (viewed as a continuous variable) for Teva's Fentanyl patch does not exceed the mean in the population for Alza's Duragesic® patch by more than 25% (i.e. $\mu_T/\mu_R \leq 1.25$.)

Study 770-0407-01 (Irritation study)
The mean total irritation score (21 daily applications) was analyzed using the mixed model. The non-inferiority test was failed for test placebo versus negative control, but passed for test placebo versus positive controls (0.02% and 0.04% Sodium Lauryl Sulfate, see Table 2.3). Thus, based on these data, we can conclude that the mean in the population for the mean total irritation score (viewed as a continuous variable) for the test placebo patch does not exceed the mean in the population for the positive controls (0.02% and 0.04%) by more than 25% (i.e. $\mu_T/\mu_R \leq 1.25$.)

Study 770-0407-03 (Sensitization)
According to the OGD medical reviewer's comments, a sensitization score ≥ 2 or a sensitization score ≥ 1 AND a *letter response* (e.g. 1P) was defined as a sensitized score. No subject had a sensitized score from the test placebo patch or negative control patch at Hour 48 and 72 in the challenge phase of this study. These reactions are not indicative of allergic contact dermatitis.

Based on the 95% upper confidence bound at hour 48 and/or 72, the Test placebo patch rate may exceed the negative control patch rate by at most 0.57 percentage points, based on the McNemar confidence bound as given by Fleiss, or 2.48 percentage points based on an alternate confidence bound method (which may be more accurate than the McNemar confidence bound when the rates are small) for the difference in sensitization rates. Note that no subjects were sensitized on the test placebo product and the negative control, out of 178 subjects at hour 48 and 179 subjects at hour 72.

_____
Huaixiang Li, Ph.D.
Mathematical Statistician, DIV 6/OB

_____
Donald J. Schuirmann
Expert Mathematical Statistician, DIV 6/OB

_____
Stella G. Machado, Ph.D.
Director, DIV 6/OB
cc:
HFD-600 Dena R Hixon, Sarah Seung, Debra M Catterson
HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li, DIV 6/OB
Lillian Patrician, OB

Appendix

Table 4.1: PP population (36 subjects) for the irritation study (770-0407-01)
Frequency of total irritation scores per visit day

Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Test placebo																					
0	36	34	30	28	20	17	10	8	13	14	11	11	9	9	7	7	6	6	3	3	3
1		2	6	8	16	19	26	25	22	20	23	23	26	26	27	27	26	25	28	28	28
2								3	1	2	2	2	1	1	2	2	4	5	5	5	5
Negative control																					
0	34	35	35	33	36	35	33	33	31	28	30	29	29	26	25	27	26	25	27	25	26
1	2	1	1	3		1	3	3	4	8	6	7	7	10	11	9	10	9	8	10	9
2									1									2	1	1	1
Positive control (0.02%)																					
0	34	26	30	29	29	28	22	15	16	11	9	6	6	4	5	1	3	3	2	2	2
1	2	10	6	7	7	8	12	21	19	25	27	30	30	31	29	32	29	29	30	28	28
2							2		1					1	2	2	3	3	3	6	6
3																1	1				
5																		1	1		
Positive control (0.04%)																					
0	31	20	18	8	4	1		1	1	1											
1	5	16	18	28	29	19	6		2	1	2	2	2	3	2	5	5	7	9	8	8
2					3	13	12	2	1	1	5	7	10	14	16	14	14	13	13	15	15
3						3	18	33	32	31	25	20	16	15	17	17	15	16	14	13	13
4												1	2	1	1		1				
5										2	4	6	6	3			1				

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

/s/

Huaixiang Li
4/1/2008 04:35:43 PM
BIOEQUIVALENCE STATISTICIAN

Donald Schuirmann
4/2/2008 09:43:01 AM
BIOMETRICS

Stella Machado
4/2/2008 11:34:58 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

OTHER REVIEWS

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170, 10903 New Hampshire Ave., Silver Spring, MD 20993

CONSULTATION

Date:	December 16, 2005
To:	Peter Chen, HFD-617 Office of Generic Drugs
Through:	Bob Rappaport, M.D. Division Director, DAARP
From:	R. Daniel Mellon, Ph.D. Supervisory Pharmacologist, DAARP
Subject:	Pharmacology Toxicology consultation on ANDA 77-449. Fentanyl Transdermal Extended-Release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day
Date of Submission:	January 30, 2004
Date Response Requested (Priority):	September 22, 2005 (Low)

Background: Teva Pharmaceuticals USA submitted ANDA 77-449 for a Fentanyl Transdermal Extended-Release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day drug products.

The Office of Generic Drug Products (OGD) requested a pharmacology toxicology review of the safety assessments for polyisobutene adhesives and (b) (4) (b) (4) and tolerance and toxicology studies for (b) (4). The consults requested the following: "Please review and provide your conclusions on the acceptability of the levels proposed in the Safety Assessments in conjunction with the data provided in the Tolerance and Toxicology Studies."

The following materials were provided for review:

1. A safety assessment for polyisobutene adhesives (b) (4) as well as (b) (4) prepared by (b) (4), a toxicology consultant.
2. A letter from (b) (4) on behalf of Teva Pharmaceuticals stating that it is their understanding that polybutenes have been used as (b) (4) in pressure sensitive adhesives of transdermal drug products.
3. Three toxicology studies of (b) (4) Polybutene products that were submitted by (b) (4) on behalf of Teva Pharmaceuticals:
   a. Subacute (90-day) Toxicology Studies on Polyolefins (b) (4)
   b. Subacute (90-day) Toxicology Studies on Polyolefins
   c. Two-Year Chronic Oral Toxicity of (b) (4) – Beagle Dogs
   d. Two-Year Chronic Oral Toxicity of (b) (4) – Albino Rats.

Pharmacology Toxicology Analysis:

Polyisobutene Adhesives (b) (4) as well as (b) (4) Safety Assessments by (b) (4)

According to the safety assessment, polyisobutene adhesives (b) (4) and Polybutene ((b) (4)) are components of the proposed transdermal patch that is designed to provide fentanyl continuously for a total of 72-hours. The assessment states that polyisobutene adhesive was tested for skin irritation potential (in New Zealand White Rabbits) and skin sensitization potential (vial local lymph node assay). In addition, polyisobutene adhesive (b) (4) and similar products of differing molecular weight, "did not possess any cytotoxic potential." Polybutene ((b) (4) (b) (4)) was considered "practically non-toxic when tested in acute oral and dermal studies in rats and rabbits, respectively."

The safety assessment further notes the following:

> The highest concentration of Polyisobutene Adhesive (b) (4) as well as Polybutene ((b) (4)) for the specific transdermal patch currently under development are as follows:
>
> (b) (4)
>
> For a 70 kg person the dosages would be:
>
> (b) (4)
>
> mg/kg/day

As the data to support the above statements were not provided, it is not possible to comment on the validity of the statements made in the safety assessment. The safety assessment refers to the highest "concentration" of (b) (4) for the transdermal product and cites mass rather than concentration. Finally, the levels proposed for a 70 kg person appears to assume that the patch is consumed entirely, which is unlikely to be the case. As the patch is removed after the 72 hours and replaced by a new patch, most of the components of the patch are likely discarded. Therefore, the dosages proposed are not relevant.

Subacute (90-day) Toxicology Studies on Polyolefins

The Sponsor provided two study reports, both dated June 1, 1962, that describe the results of 90-day oral toxicity studies on four polyolefins in rats bred in the (b) (4) (b) (4). According to the materials provided, these studies were completed for (b) (4) to support a proposal that polyisobutenes may be safety used in the manufacture of (b) (4) articles that contact food.

The test articles were administered via the diet and are listed in the table below:

Material Tested	*Dose (Dietary)*
(b) (4)	5%
	5%
	5%
	5%

Overall, these two studies do not provide useful information regarding the potential safety of the three components of the patch for the following reasons:

1. the studies do not assess the safety of the dermal route of administration,
2. the materials tested are not the same as the materials proposed materials,
3. the studies did not determine the actual dose of the materials the rats consumed, and,
4. the studies do not appear to have been conducted under Good Laboratory Practice Guidelines.

Two-Year Chronic Oral Toxicity of (b) (4) – Albino Rats (b) (4) (b) (4).

The Sponsor submitted a copy of a "Report to (b) (4) Two-Year Chronic Oral Toxicity of (b) (4) – Albino Rats" that was prepared by (b) (4).

Two-Year Chronic Oral Toxicity of (b) (4) – Beagle Dogs

The Sponsor submitted a copy of a "Report to (b) (4) Two-Year Chronic Oral Toxicity of (b) (4) – Beagle Dogs" that was prepared by (b) (4). The report does not include a signature page and therefore is not dated. Based on the similarity to the rat study report, the report was likely completed around the same time frame as the rat study (b) (4).

(b) (4) were determined to be invalid and had to be repeated. It is not clear if the studies submitted were evaluated and determined to be valid assays or should also be considered suspect.

As was the case with the 90-day toxicity studies, the two-year toxicology studies do not provide useful information regarding the potential safety of the three components of the patch for the following reasons:

1. the studies do not assess the safety of the dermal route of administration,
2. the materials tested are not the same as the materials proposed materials,
3. the studies did not determine the actual dose of the materials the rats consumed, and,
4. the studies were not conducted under Good Laboratory Practice Guidelines (b) (4).

Conclusion:

Following review of the materials provided, it is my opinion that the safety assessment completed by the Sponsor's toxicology consultant are not adequate for a dermal application, and that the submitted toxicology studies are not supportive of the materials present in the drug product.

Additional Comments to OGD:

In the process of reviewing the materials provided and materials I obtained to assist this review, I suspect that the materials in question may already be used in approved products. This should be confirmed by the Chemistry Review Team. Specifically, please note that the approved labeling for the Nicotrol Nicotine Transdermal System lists the following inactive ingredients: **polyisobutylenes, polybutene** non-woven polyester, pigmented aluminized and clear polyesters.

Likewise, the middle layer of Ortho Evra® (norelgestromin / ethinyl estradiol) Transdermal System contains, among other components, **polyisobutyene/polybutene**

adhesive. Polyisobutylene is also a component of the adhesive layer of the Vivelle® (estradiol transdermal system).

If the materials proposed for use in this ANDA be the same as those found in the approved referenced products above, the question of the adequacy of the Sponsor's safety assessment would become moot.

#113 3.1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
TO *(Division/Office)* DACCADP HFD-170 Thru Leah Ripper ODE II HFD-102	FROM: Kojo Awuah, OGD/DLPS/Regulatory Support Branch HFD—617 Thru Peter Chen OGD/DLPS/RSB HFD-617

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06/22/05		77-449	New Correspondence	June 15, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fentanyl Transdermal Extended-release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day	LOW	Narcotic/Analgesic	September 22, 2005

NAME OF FIRM Teva Pharmaceuticals USA

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL
9 PROGRESS REPORT
9 NEW CORRESPONDENCE
9 DRUG ADVERTISING
9 ADVERSE REACTION REPORT
9 MANUFACTURING CHANGE/ADDITION
9 MEETING PLANNED BY _____
9 PRE NDA MEETING
9 END OF PHASE II MEETING
9 RESUBMISSION
9 SAFETY/EFFICACY
9 PAPER NDA
9 CONTROL SUPPLEMENT
9 RESPONSE TO DEFICPENCY LETTER
9 FINAL PRINTED LABELING
9 LABELING REVISION
9 ORIGINAL NEW CORRESPONDENCE
9 FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END QF PHASE II MEETING 9 CONTROLLED STUDI ES 9 PROTOCOL REVIEW 9 OTHER	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION
□ PROTOCOL-- BIOPHARMACEUTICS
□ IN--VIVO WAIVER REQUEST
□ DEFICIENCY LETTER RESPONSE
□ BIOAVAILABILITY STUDIES
□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

x□ CLINICAL □ PRECLINICAL

COMMENTS

OGD is requesting a Pharm/Tox Review. Included are Safety Assessments for Polyisobutene Adhesives and (b) (4) and Tolerance and Toxicological Studies for (b) (4). Please review and provide your conclusions on the acceptability of the levels proposed in the Safety Assessments in conjuction with the data provided in the Tolerance and Toxicological Studies. Your input is very much appreciated.

Thank you,

Kojo

Please provide as electronic transfer of the completed review and return to Peter Chen HFD-617

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)*
Kojo Awuah	□ MAIL □ HAND
GNATURE OF RECEIVER	SIGNATURE OF DELIVERER

RECEIVED
JUN 24 2005
OFFICE OF DRUG EVALUATION II

FORM FDA 3291 (7/83)
V:\FIRMSNZ\TEVA\LTRS&REV\77449-toxconsult-23June2005.DOC
cc: ANDA 77-449

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170, 10903 New Hampshire Ave., Silver Spring, MD 20993

CONSULTATION

Date:	August 1, 2007
To:	Ted Palat, HFD-617 Office of Generic Drugs
Through:	Bob Rappaport, M.D. Division Director, DAARP
From:	R. Daniel Mellon, Ph.D. Supervisory Pharmacologist, DAARP
Subject:	Pharmacology Toxicology consultation #2 on ANDA 77-449. Fentanyl Transdermal Extended-Release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day re safety of (b) (4)
Date of Submission:	April 4, 2007
Date Response Requested (Priority):	July 3, 2007 (90-days) – extended following discussion with OGD.

Background: Teva Pharmaceuticals USA submitted ANDA 77-449 for a Fentanyl Transdermal Extended-Release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day, and 2.4 mg/day drug products.

The consult requested the following:

> The Office of Generic Drug Products (OGD) requested a pharmacology toxicology review of the data submitted by (b) (4) and (b) (4) on behalf of TEVA Pharmaceuticals. This information was submitted in response to the conclusions from the pharmtox consult dated December 16, 2005. Please provide your conclusions on the acceptability of the

levels of proposed in the Safety Assessments in conjunction with the data in the additional toxicology information. A copy of the first pharmtox consult is included for your reference. Please cc Benjamin Danso, HFD-617 (Benjamin.danso@fda hhs.gov) on the review when it is being checked into DFS. Thank you.

As noted above, this is the second consultation regarding the use of the excipient in this ANDA. The following materials were reviewed as part of the 2005 original consultation request:

1. A safety assessment for polyisobutene adhesives (b) (4) as well as (b) (4) prepared by (b) (4), a toxicology consultant.
2. A letter from (b) (4) on behalf of Teva Pharmaceuticals stating that it is their understanding that polybutenes have been used as (b) (4) in pressure sensitive adhesives of transdermal drug products.
3. Three toxicology studies of (b) (4) Polybutene products that were submitted by (b) (4) on behalf of Teva Pharmaceuticals:
   a. Subacute (90-day) Toxicology Studies on Polyolefins (b) (4)
   b. Subacute (90-day) Toxicology Studies on Polyolefins
   c. Two-Year Chronic Oral Toxicity of (b) (4) – Beagle Dogs
   d. Two-Year Chronic Oral Toxicity of (b) (4) – Albino Rats.

The 2005 response provided to OGD was as follows:

Conclusion:

Following review of the materials provided, it is my opinion that the safety assessment completed by the Sponsor's toxicology consultant are not adequate for a dermal application, and that the submitted toxicology studies are not supportive of the materials present in the drug product.

Additional Comments to OGD:

In the process of reviewing the materials provided and materials I obtained to assist this review, I suspect that the materials in question may already be used in approved products. This should be confirmed by the Chemistry Review Team. Specifically, please note that the approved labeling for the Nicotrol Nicotine Transdermal System lists the following inactive ingredients: **polyisobutylenes**, **polybutene** non-woven polyester, pigmented aluminized and clear polyesters.

Likewise, the middle layer of Ortho Evra® (norelgestromin / ethinyl estradiol) Transdermal System contains, among other components, **polyisobutyene/polybutene adhesive**. **Polyisobutylene** is also a component of the adhesive layer of the Vivelle® (estradiol transdermal system).

If the materials proposed for use in this ANDA be the same as those found in the approved referenced products above, the question of the adequacy of the Sponsor's safety assessment would become moot.

During the review of the materials in the current consultation request, I spoke with Dr. Glen Smith, the chemistry team leader on OGD, to further explore the possibility that the excipient in question was actually already found in approved FDA dermal products and therefore is not novel. Dr. Smith was able to conclude that the polymeric adhesive is used in a wide variety of dermal products. Therefore, we agreed that the only potential pharmacology toxicology issue that remained regarding the safety of the polymeric material would be related to levels of the residual monomers in the polymeric materials, (b) (4) and (b) (4)

Specific levels of residual monomers have not been provided in the consult request. As both (b) (4) and (b) (4) appear to be gases at room temperature, the levels of monomers in the polymeric material are likely to be low. Nonetheless, the existing key genotoxicity and carcinogenicity data in the published literature for these potential residual monomers are summarized below:

(b) (4)

According to the data in the ToxNet Database, (b) (4)

The NTP also completed chronic inhalation toxicology studies with this compound and reported negative results in the male mouse, the female mouse, and the female rat, with equivocal findings in the male rat (National Toxicology Program, 1998). Collectively, these data with the purified monomers suggest negligible concern regarding risk associated with exposure to residual (b) (4) monomers in the adhesive employed by TEVA for this product.

(b) (4)

According to the data in the NTP Database, [redacted]. Based upon a literature review, there does not appear to any carcinogenicity assessment of [redacted] as a monomer in the literature.

Recommendation: From the nonclinical pharmacology and toxicology perspective, there does not appear to significant safety concerns with the use of [redacted] in the TEVA fentanyl patch product, assuming the manufacturer of the [redacted]) sets specifications for residual monomer levels [redacted] within those of the already FDA-approved products. The dermal safety of this excipient appears to be supported by the following:

1) The existing clinical use of this material via comparable routes of administration,
2) the [redacted] suggesting low levels of residual monomers,
3) the existing negative mutagenicity data (Ames assay only) for the purified monomers, and,
4) the overall lack of carcinogenic potential of the [redacted] monomer.

Reference List

[redacted]

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

/s/

R. Daniel Mellon
8/1/2007 09:58:06 AM
PHARMACOLOGIST

Bob Rappaport
8/1/2007 01:12:13 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-449

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 8642
FAX: (215) 591 8812

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

December 17, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Fentanyl Transdermal System, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h.

Enclosed are archival and review copies assembled in accord with the Office of Generic Drugs' February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 27 volumes; 13 for the archival copy and 14 for the review copy.

The application contains a full report of one *in vivo* bioequivalence study. This study compared Fentanyl Transdermal Stystem, 25 µg/h manufactured for TEVA Pharmaceuticals USA to the reference listed drug, DURAGESIC®, 25 µg/h. Additionally, we have included reports of a skin irritation study and a sensitization study.

Two separately bound copies of the drug substance and finished product analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-8642 or by facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/jmd
Enclosures

RECEIVED
DEC 20 2004
OGD / CDER

ANDA 77-449 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

RTR 4) Check that correct letter format is used. (PTV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Duragesic

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Duragesic 19-813

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

___ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ___yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Marlie A Gurian date 7 Feb 2005

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-449 **FIRM NAME:** TEVA PHAMACEUTICALS USA

RELATED APPLICATION(S): NA

First Generic Product Received? NO

Bio Assignments:		Micro Review
☒ BPH	☒ BCE	☐
☒ BST	☐ BDI	

DRUG NAME: FENTANYL

DOSAGE FORM: FILM EXTENDED RELEASE TRANSDERMAL
25 UG/HR = 0.6 MG/24HR
50 UG/HR = 1.2 MG/24HR
75 UG/HG = 1.8 MG/24HR
100 UG/HR = 2.4 MG/24 HR

Random Queue: 9
Chem Team Leader: Smith, Glen J PM: Ted Palat Labeling Reviewer: Chan Park

Letter Date: DECEMBER 17, 2004	**Received Date:** DECEMBER 20, 2004
Comments: EC - 4 YES **On Cards:** YES **Therapeutic Code:** 2030200 NARCOTIC ANALGESICS	
Archival Format: PAPER **Sections** **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Kwadwo Awuah **Date** 2/1/05	**Recommendation:** ☐ **FILE** ☒ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 7 Feb 2005
ADDITIONAL COMMENTS REGARDING THE ANDA:	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES Phone (215) 591-3000 (Statement regarding Rx/OTC Status) RX YES Contact Person: Vincent Andolina	☑
Sec. II	**Basis for Submission** **NDA# : 19-813** Ref Listed Drug: DURAGESIC Firm: ALZA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☑
Sec. III	**Patent Certification** 1. Paragraph: III 2. Expiration of Patent: 1-23-2005 A. Pediatric Exclusivity Submitted? PED Exclusivity expires 11/20/06 B. Pediatric Exclusivity Tracking System checked? YES **Exclusivity Statement:** YES NPP Exclusivity Expires 5/20/06 ↳ New Pt Population (NPP) Exclusivity Carved Out.	☑
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same except for NPP Exclusivity info 2. Active ingredients Fentanyl 3. Route of administration Transdermal 4. Dosage Form Extended-release Film 5. Strength 25 µg/hr, 50µg/hr, 75µg/hr and 100 µg/hr	☑
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL (4 copies of draft) 2. 1 RLD label and 1 RLD container label ✓ (PI is electronic) 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☑
Sec. VI	**Bioavailability/Bioequivalence** → Firm has to provide this form **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO **2. Request for Waiver of In-Vivo Study(ies): YES ON 50, 75, AND 100UG/HG** (Page 2344) **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) YES **4. Lot Numbers of Products used in BE Study(ies):** ANDA Lot # 77082/ RLD 0323963 **5. Study Type:** (Continue with the appropriate study type box below)	☐
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) – YES (Page 163) b. EDR Email: Data Files Submitted: c. In-Vitro Dissolution: YES –	☑

Info in transdermal delivery System section.

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** YES a. In-Vivo PK Study YES STU/BIO STU/DR. HIXON (CLINICAL) 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution YES 3. EDR Email: Data Files Submitted YES SENT TO EDR b. Adhesion Study YES c. Skin Irritation/Sensitization Study YES – Results OK as per Dr. Krista Scardina (1/31/05)	☑
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation – pages 2895+ 2. Inactive ingredients as appropriate – No Justification given for Inactive Ingredients. Inactive Ingredients used in drug product not previously approved for use in a transdermal product.	☐

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers — (Page 2910) b. Type II DMF authorization letters or synthesis (DMF # (b) (4) redacted c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers – (b) (4) redacted 2. **Inactive Ingredients** a. Source of inactive ingredients identified – (Page 3007) b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓	☑
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES ✓ 3. CFN numbers - 1058791	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers ✓	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓ 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement (page 3417)	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data ✓ Missing Batch Records for lot #'s 33945, 33946 & 33947	☐
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address — (page 3007)	☑

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data ✓ 2. Certificate of Analysis for Finished Dosage Form ✓	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted ✓ a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Has to be Revised 2. Finished Dosage Form 3. Same lot numbers	☐
Sec. XVII	**Environmental Impact Analysis Statement**	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☑

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-449

FEB 09 2005

TEVA Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 17, 2004, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fentanyl Transdermal Extended-release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> It appears that your proposed drug product contains the following inactive ingredients; Polyisobutene Adhesive (b) (4) and Polyester Release Liner (b) (4) which have not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. According to the regulation, there is reasonable basis to conclude that the inactive ingredients in your proposed product may raise safety questions because of the lack of information that you have provided regarding their use. The Office of Generic Drugs (OGD) will not file this application as an ANDA since new inactive ingredients must be the subject of a new drug application. Please provide additional information to support the safety of the use of these inactive ingredients in your proposed drug product. The information to demonstrate safety should include, but is not limited to, examples of approved drug products administered by the same route of administration which contains the same inactive ingredient within the same concentration range.

Also, the concentration of the inactive ingredients Polybutene [redacted] (b)(4) and Isopropyl Myristate in your proposed product exceeds the maximum concentration at which these inactive ingredients have been previously approved by the Agency in a transdermal drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration, which contain this inactive ingredient in the same concentration range.

You have failed to provide complete batch records for executed Lot numbers 33945, 33946 and 33947.

Please provide a Financial Certification Form (FDA 3454) for each study that was completed in support of this ANDA.

Please provide a revised statement pertaining to the availability and identification of samples of the drug substance and finished dosage form for your ANDA.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Kojo Awuah
Project Manager
(301) 827-5862

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-449
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 2/8/05
HFD-615/KAwuah, CSO _____ date 2/8/05
Word File
V:/FIRMSAM/TEVA/LTRS&REV/77449.RTR
F/T by KAA 2/8/05
ANDA Refuse to Receive!

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Direct Dial: (215) 591 8642
Direct FAX: (215) 591 8812
vincent.andolina@tevausa.com

ORIG AMENDMENT

N/AC

March 21, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT TO A
"REFUSE-TO-RECEIVE" APPLICATION

ANDA 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
AMENDMENT

Dear Mr. Buehler:

We submit herewith an amendment pursuant to 21 CFR §314.101(b)(3) (ii) to our ANDA 77-449 for Fentanyl Transdermal System, 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h.

This submission addresses the Agency's February 9, 2005 letter refusing to receive this ANDA under 21 CFR §314.101(d)(3). A copy of the Agency's letter is enclosed **(Attachment 1)**.

The Agency's comments are reproduced below and Teva's responses follow.

> It appears that your proposed drug product contains the following inactive ingredients: Polyisobutene Adhesive (b) (4) and Polyester Release Liner (b) (4) which have not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. According to the regulation, there is reasonable basis to conclude that the inactive ingredients in your proposed product may raise safety questions because of the lack of information that you have provided regarding their use. The Office of Generic Drugs (OGD) will not file this application as an ANDA since new inactive ingredients must be the subject of a new drug application. Please provide additional information to support the safety of the use of these inactive ingredients in your proposed drug product. The information to demonstrate safety should include, but is not limited to, examples of approved drug products administered by the same route of administration which contains the same inactive ingredient within the same concentration range.

The polyisobutene adhesives are listed in FDA's inactive ingredient database under the synonym polyisobutylene (CAS No. 009003274) with a maximum "potency" of 119 mg.

Our proposed drug product exposes the patient to less than 119 mg per day of each of the polyisobutene adhesives (b) (4) since each unit is intended to be worn for 72 hours.

Please refer to **Attachment 2** for a copy of a report from our toxicology consultant, (b) (4) (b) (4). Dr. (b) (4) has evaluated the safety of the proposed polyisobutene adhesives, (as well as polybutene which is addressed below) and concluded that the concentrations of these materials in Teva's proposed formulation given to a 70 kg person over 72 hours, would not be expected to cause any adverse effect.

With regard to the Polyester Release Liner, it is peeled from the patch prior to application. Patients are not exposed to this material.

> Also, the concentration of the inactive ingredients Polybutene ((b) (4) and Isopropyl Myristate in your proposed product exceeds the maximum concentration at which these inactive ingredients have been previously approved by the Agency in a transdermal drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration, which contain this inactive ingredient in the same concentration range.

Dr. (b) (4) has evaluated the safety of the proposed polybutene (b) (4), (as well as the polyisobutenes which are addressed above) and concluded that the concentrations of this material given to a 70 kg person over 72 hours would not be expected to cause any adverse effect. A copy of Dr. (b) (4) s report is enclosed (**Attachment 2**).

With regard to the isopropyl myristate, the Agency's inactive ingredient database permits a maximum "potency" of 10% of this inactive ingredient in other topical dosage forms (topical; emulsion, cream and topical; gel). Please refer to **Attachment 3** for our toxicology consultant Dr. (b) (4) 's safety evaluation of isopropyl myristate. Dr. (b) (4) concluded that no adverse effect would be expected at the proposed concentration of isopropyl myristate to a 70 kg person over 72 hours.

In addition, our original ANDA pages 2389 to 2891 contained results of skin irritation and skin sensitization studies (performed using placebo patches). The irritation study report stated that this product exhibits only slight potential for very mild cumulative irritation. The sensitization study report stated that most subjects exhibited either no visible erythema or mild erythema during the induction phase, and no subjects exhibited scores indicative of allergic contact dermatitis at the challenge phase.

> You have failed to provide complete batch records for executed Lot numbers 33945, 33946 and 33947.

Batch records for executed lot numbers 33945, 33946 and 33947 were not submitted with the original ANDA because the (b) (4) utilized for those lots is not being proposed in the ANDA. However, as requested, please refer to **Attachment 4** for the executed batch records for lot numbers 33945, 33946 and 33947.

Please provide a Financial Certification Form (FDA 3454) for each study that was completed in support of this ANDA.

Please refer to **Attachment 5** for copies of Financial Certification Forms (FDA 3454) for each clinical study that was completed in support of this ANDA. These financial certification forms were included in Section 6.1 (pages 121-139) of our original ANDA.

Please provide a revised statement pertaining to the availability and identification of samples of the drug substance and finished dosage form for your ANDA.

Please refer to **Attachment 6** for a revised sample availability statement.

We look forward to your review and acceptance of our application. Should there be any questions regarding this information, please contact the undersigned by phone at (215) 591-8642 or by facsimile at (215) 591-8812.

Sincerely,

for VA

VA/va
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Direct Dial: (215) 591 8642
Direct FAX: (215) 591 8812
vincent.andolina@tevausa.com

April 20, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT TO A
"REFUSE-TO-RECEIVE" APPLICATION

ORIG AMENDMENT
N/AC

ANDA 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
AMENDMENT

Dear Mr. Buehler:

We submit herewith an amendment pursuant to 21 CFR §314.101(b)(3) (ii) to our ANDA 77-449 for Fentanyl Transdermal System, 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h.

This submission is in response to Teva's telephone conversations of April 13, 2005 with Kwadwo Awuah, Pharm.D., Project Manager, Regulatory Support Branch.

Dr. Awuah indicated that in response to Teva's March 21, 2005 Amendment, this application remained in Refuse-to-Receive status due to concern regarding possible leaching from the polyester release liner prior to use of the product. (The release liner is removed prior to application of the transdermal system.)

The release liner is listed in FDA's inactive ingredient database under "Silicone/Polyester Film Strip" with a maximum "potency" of 873 mg for Transdermal; Film, Controlled-Release.

The "Silicone /Polyester Film Strip" content of each of the fentanyl units is well within the IIG limits, as shown in the table below.

Size	Strength (per hour)	mg of Silicone/Polyester Film
10.7 cm^2	25 µg	(b) (4)
21.4 cm^2	50 µg	
32.1 cm^2	75 µg	
42.8 cm^2	100 µg	

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APR 2 1 2005
OGD / CDER

Accordingly, we hereby request that our ANDA be accepted for filing, since there are no remaining IIG issues that could preclude its acceptance.

We look forward to your review and acceptance of our application. Should there be any questions regarding this information, please contact the undersigned by phone at (215) 591-8642 or by facsimile at (215) 591-8812.

Sincerely,

VA/va
Enclosures

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-449 **FIRM NAME:** TEVA PHAMACEUTICALS USA

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: FENTANYL

DOSAGE FORM: FILM EXTENDED RELEASE TRANSDERMAL
25 UG/HR = 0.6 MG/24HR
50 UG/HR = 1.2 MG/24HR
75 UG/HG = 1.8 MG/24HR
100 UG/HR = 2.4 MG/24 HR

Bio Assignments:		Micro Review
☒ BPH	☒ BCE	☐
☒ BST	☐ BDI	

Random Queue: 9
Chem Team Leader: Smith, Glen J PM: Ted Palat Labeling Reviewer: Chan Park

Letter Date: DECEMBER 17, 2004	**Received Date:** DECEMBER 20, 2004
Comments: EC - 4 YES **On Cards:** YES **Therapeutic Code:** 2030200 NARCOTIC ANALGESICS	
Archival Format: PAPER **Sections** **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST **Kwadwo Awuah** **Date** **4/27/05**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____
ADDITIONAL COMMENTS REGARDING THE ANDA: **Consults had to sent for the following inactive ingredients: Polyisobutene Adhesive, Polybutene and Isopropyl Myristate. Please see page 6 of this checklist for any questions about the Inactive Ingredients. The safety assessments for the Inactive Ingredients listed above can be found in Vol 2.1 as a response to a "RTR". Please see "Refuse to Receive" letter for deficiencies.**	
Top 200 Drug Product:	

6/1/05 vincent mdolkia

21180 ortho EVRA

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES Contact Person: Vincent Andolina Phone: (215) 591-3000	☒
Sec. II	**Basis for Submission** **NDA# : 19-813** Ref Listed Drug: DURAGESIC Firm: ALZA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: III 2. Expiration of Patent: 1-23-2005 A. Pediatric Exclusivity Submitted? PED Exclusivity expires 11/20/06 B. Pediatric Exclusivity Tracking System checked? YES **Exclusivity Statement:** YES (New Patient Population (NPP) Exclusivity carved out of labeling).	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same except for NPP Exclusivity Info. (carved out of labeling) 2. Active ingredients Fentanyl 3. Route of administration Transdermal 4. Dosage Form Extended-release Film 5. Strength 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL (4 copies of draft) 2. 1 RLD label and 1 RLD container label YES (Patient Package Insert is electronic) 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): YES ON 50, 75, AND 100UG/HG (page 2344+)** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Parenterals) NA **4. Lot Numbers of Products used in BE Study(ies):** ANDA Lot # 77082 / RLD Lot # 0323963 **5. Study Type:** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: c. In-Vitro Dissolution: YES	☐

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** YES a. In-Vivo PK Study YES STU/BIO STU/DR. HIXON (CLINICAL) 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) YES (page 163) 2. In-Vitro Dissolution YES – located in the transdermal delivery section 3. EDR Email: Data Files Submitted YES SENT TO EDR b. Adhesion Study YES c. Skin Irritation/Sensitization Study YES – Results OK as per Dr. Krista Scardina (1/31/05)	☒
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation (pages 2895 +) 2. Inactive ingredients as appropriate – Safety assessments were sent in for Polyisobutene Adhesive Polybutene and Isopropyl Myristate. The safety assessments will be sent on consult as per Dr. Glen Smith, TEVA also sent in an amendment (response to a RTR - Vol 2.1) which was evaluated by Dr. Shahnaz Read. Her comments have been included under the IIG search table which has been attached to this checklist as page 6.	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers (page 2910) b. Type II DMF authorization letters or synthesis (DMF # (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis YES e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers (b) (4) 2. **Inactive Ingredients** a. Source of inactive ingredients identified (page 3007) b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers 1058791	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers YES	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / Terminal sterilization NA 4.Filter validation (if aseptic fill) NA 5. Reprocessing Statement (page 3417)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES – page 3421 2. In-process Controls - Specifications and data YES	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address (page 3007)	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period 24 months 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: Revised version in amendment (Vol 2.1) 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers YES	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☒

INACTIVE INGREDIENT SEARCH TABLE
ON NEXT PAGE

INACTIVE INGREDIENT SEARCH TABLE

Fentanyl Transdermal Extended-release Film, 0.6 mg, 1.2 mg, 1.8 mg and 2.4 mg per day
ANDA 77-449, 4/26/05

OCTYLDODECANOL	TRANSDERMAL; FILM, CONTROLLED RELEASE	(b) (4)	253.4MG ✓
SILICONE/POLYESTER FILM STRIP	TRANSDERMAL; FILM, CONTROLLED RELEASE		873.0MG ✓
POLYISOBUTYLENE	TRANSDERMAL; FILM, CONTROLLED RELEASE		119.0MG

As per Dr. Shahnaz Read who reviewed the response/amendment to the "Refuse to Receive", Polyisobutene is chemically the same as Polyisobutylene (CAS # 009003274) so the IIG limits for Polyisobutylene will apply to Polyisobutene as long as any additives are justified. The IIG limit for this inactive ingredient is 119 mg per day which is used in (b) (4). The proposed drug product will expose the patient to (b) (4) mg of Polyisobutylene per day which is higher than the previously approved limit, however, the applicant sent in some safety assessments which can be sent on consult as per Dr. Read (4/11/05).

Polybutene (Hydrogenated Polyisobutene) has been previously approved for use in (b) (4); however, the potency/quantity of this inactive that was used was not given as per COMIS. The safety assessment for this inactive was sent in with the assessment for Polyisobutylene mainly because (b) (4) (b) (4) The safety assessment for Polybutene will be sent on consult as well. The proposed level of Polybutene for this ANDA is (b) (4) for 3 days.

Dr. Read also stated that the limit in the IIG for Isopropyl Myristate for Topicals should be applicable to the limit for Transdermal drug products. The limit for Isopropyl Myristate in a previously approved Topical drug product is 10 gm and the proposed level for this ANDA (b) (4).

Regarding the Release liners, Dr. Read stated that toxicological studies should be provided to show that any additives on the Release liners are safe since they are in contact with the skin contact side of the system. She suggested that the information may be available from the manufacturer of the Release liner. After talking to Vincent Andolina from TEVA on 4/13/05, the firm sent in an amendment stating that the release liner has been previously approved for use in transdermal drug product. The IIG limit is posted in the table above.

OGD Template Revised 04/01/2004 /T.Hinchliffe

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

June 13, 2005

THIRD PARTY SUBMISSION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 μg/h, 50 μg/h, 75 μg/h and 100 μg/h
NEW CORRESPONDENCE - THIRD PARTY SUBMISSION

Dear Mr. Buehler:

We submit herewith correspondence to the above-referenced ANDA which was submitted on December 17, 2004, pursuant to 21 CFR §314.101(b)(3) (ii). This submission is in response to refusal to file letters received with respect to this application, and in response to a conversation between Martin Shimer of the Regulatory Support Branch and Jill Pastore of TEVA Pharmaceuticals USA on June 10, 2005. Specifically, we hereby grant authority to (b) (4) to submit confidential information to this ANDA on behalf of TEVA to complete review of this application for filing.

As background, TEVA's application remains in Refuse-to-Receive status due to concern regarding possible leaching from the polyester release liner prior to use of the product (said release liner is removed prior to application of the transdermal system). (b) (4) is the supplier of the (b) (4) that is of concern. Therefore, in order to expedite acceptance of this ANDA for review by the Agency, (b) (4) will submit sub-chronic and chronic toxicity studies conducted for (b) (4) directly to the Agency for TEVA's ANDA. TEVA hereby grants (b) (4) the authority to submit such data as a confidential submission to ANDA 77-449.

We look forward to your review and acceptance of our application. Should there be any questions regarding this information, please contact the undersigned by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
JUN 1 4 2005
OGD / CDER

ANDA 77-449

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

JUN 30 2005

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the "Refuse to Receive" Letter dated February 9, 2005 and to your amendments dated March 21 and June 13, 2005. Reference is also made to the correspondence submitted by [redacted] (b) (4) dated June 15, 2005.

NAME OF DRUG: Fentanyl Transdermal Extended-release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day.

DATE OF APPLICATION: December 17, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 16, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ted Palat
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-449
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 30 June 05
HFD-615/KAwuah, CSO _____ date 6/30/05
Word File
V:\FIRMSAM\TEVA\LTRS&REV\77449.ACK
F/T by KAA June 30, 2005

ANDA Acknowledgment Letter!

ANDA 72-449 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. DURAGESIC PATCH

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission.

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ____yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Rapp date 30 June 2005

ANDA 77-449

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

JUL 29 2005

Dear Sir:

This letter is a correction to our June 30, 2005 acknowledgment letter. The date of acknowledgement of your abbreviated new drug application has been corrected from June 16, 2005 to March 22, 2005 in our records.

NAME OF DRUG: Fentanyl Transdermal Extended-release Film, 0.6 mg/day, 1.2 mg/day, 1.8 mg/day and 2.4 mg/day.

DATE OF APPLICATION: December 17, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 22, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ted Palat
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-449
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 29 July 05
HFD-615/KAwuah, CSO _____ date 7/29/05
Word File
V:\FIRMSAM\TEVA\LTRS&REV\77449.ACK (corrected)
F/T by KAA July 28, 2005

ANDA Acknowledgment Letter!

ARCHIVAL COPY

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

N/MC

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

August 2, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 μg/h, 50 μg/h, 75 μg/h and 100 μg/h
TELEPHONE AMENDMENT – COMPANY NAME CLARIFICATION

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a telephone request made by Dr. Awuah of the Office of Generic Drugs on July 28, 2005. Specifically, clarification was requested regarding the name of the company corresponding to the Miramar (Florida) site listed in the original ANDA application.

Please find attached, a letter from Aveva Drug Delivery Systems, Inc. which details the July 9, 2003 acquisition and name change of the Miramar (Florida) R&D/manufacturing site from Elan Transdermal Technologies to Aveva Drug Delivery Systems, Inc.

This information is submitted toward the review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

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philip.erickson@tevausa.com

August 11, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE - SUBMISSION OF PACKAGED PLACEBO SAMPLES

MC

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 μg/h, 50 μg/h, 75 μg/h and 100 μg/h
NEW CORRESPONDENCE – SUBMISSION OF PACKAGED PLACEBO SAMPLES

Dear Mr. Buehler:

We submit herewith new correspondence to our above referenced pending ANDA in response to a telephone request made by Ted Palat of the Office of Generic Drugs on August 1, 2005. Specifically, TEVA was asked to provide packaged placebo samples for evaluation of the packaging.

Please find enclosed 10 packaged placebo samples for each patch size. This packaging is representative of each strength proposed in this application.

These samples are submitted in response to the request for packaged placebo samples. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson RY

PE/jmd
Enclosures

Hixon

4.1

MEMORANDUM

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

DATE: October 3, 2005

TO: Directors, Investigations Branch

Los Angeles District Office
19701 Fairchild
Irvine, CA 92612-2445

Minneapolis District Office
240 Hennepin Avenue
Minneapolis, MN 55401

FROM: C.T. Viswanathan, Ph.D. CTV 10/05/05
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2005, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 77-449
DRUG: Fentanyl Transdermal System, 25, 50, 75 and 100 µg/h
SPONSOR: Teva Pharmaceuticals
CONTACT: Vincent Andolina
TEL: 215-591-3000
FAX: 215-591-8812

This memo requests that you arrange for inspections of the following skin irritation and sensitization studies at your respective district.

Study: Protocol 770-0407-01 - A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Healthy Adult Subjects.

Clinical Site: PRACS Dermatology, LLC
15222-B Avenue of Science
San Diego, CA 92128
TEL: (858) 618-1328
FAX: (858) 618-1058

Clinical Investigator: Robert Harper, Ph.D.

# of Subjects: 37

This was a single-center, single blind (skin evaluator was blinded), multiple-application, cumulative irritation study of a placebo transdermal delivery system (TDS). Healthy adult subjects had one placebo patch, one negative control patch (0.9% sodium chloride) and two positive control patches (0.02% and 0.04% sodium lauryl sulfate) applied daily to the upper back for 21 consecutive days. Dermal response was rated using a scoring scale.

Study: Protocol 770-0407-03 - Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects.

Clinical Site: PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104
TEL: (701) 239-4750
FAX: (701) 239-4955

Clinical Investigator: Alan K. Copa, Pharm.D.

# of Subjects: 220

This was a single-center, single blind (skin evaluator was blinded), multiple-application, repeat insult patch test of the placebo transdermal system (TDS). Healthy adult male and female subjects had one placebo TDS applied three times a week for a total of 9 applications (induction phase) and one TDS applied following a two week rest period (challenge phase). Dermal reactions were rated using a scoring scale and a scale describing features indicative of irritation (e.g., edema).

Please check the batch numbers of both the test and the reference drug formulations used in the above two studies with descriptions in the documents submitted to the Agency. Please have the records of all study subjects audited, including 100% of the informed consent forms. For both studies, **please determine if the patients met the protocol inclusion/exclusion criteria.** The subject records in the ANDA submission should be compared to the original documents at the firm. In addition to

the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were applied to the subjects as described in the study protocols. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Following the identification of the ORA investigator, background material will be forwarded directly. The ORA investigator should contact headquarters prior to the investigation in order to discuss inspection strategy and additional information. **A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: John A. Kadavil, Ph.D.
(301) 594-1048

cc:
HFD-45/RF
HFD-48/Kadavil(2)/Himaya/CF
HFD-600/Hixon
HFD-613/Catterson
HFR-PA2565/Koller (BIMO, please fax)
HFR-CE850/Matson (BIMO, please fax)
Draft: JAK 10/3/05
Edit: MKY 10/3/05
DSI: 5640 O:\BE\assigns\bio77449.doc
FACTS 677042

MINOR AMENDMENT

#1

ANDA 77-449

NOV 16 2005

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Teva Pharmaceuticals

TEL: 215.591.3141

ATTN: Philip Erickson

FAX: 215.591.8812

FROM: Ted Palat

PROJECT MANAGER: (301) 594-0338

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 17, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

Apr. 1 20, 2005 (DN) 11/25/05

Reference is also made to your amendment dated March 21 and June 13, 2005.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Following this page, 2 pages withheld in full - (b)(4)

Ce

2. The labeling, bioequivalence and clinical (skin irritation and wear studies) portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

February 24, 2006

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

RECEIVED
FEB 27 2006
OGD/CDER

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
MINOR AMENDMENT - RESPONSE TO NOVEMBER 16, 2005 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated November 16, 2005. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

A. Deficiencies

1. Please note that since we do not consider the (b) (4)

2. We have revised the listed (b) (4) and is provided as **Attachment 3**.

3. Please note that AVEVA does not receive the (b) (4)

Following this page, 3 pages withheld in full - (b)(4)

B. Comments

1. Please find enclosed, in **Attachment 17**, all currently available drug product room temperature stability data.

2. We note and acknowledge that the labeling, bioequivalence and clinical (skin irritation and wear studies) portions of our application are under review and that deficiencies, if any, will be communicated under separate cover. Please note that our response to a September 20, 2005 labeling review letter will be submitted under separate cover.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/pe

PE/jmd
Enclosures

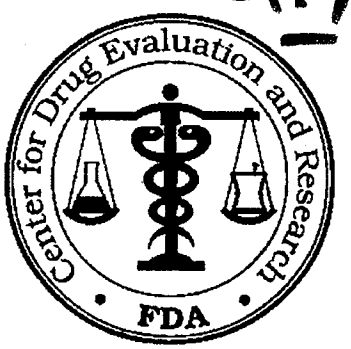
BIOEQUIVALENCY AMENDMENT

9.1

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 1 2 2006



APPLICANT: Teva Pharmaceuticals TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Keri Suh PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 21, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached two pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit the following in connection with the bioanalytical method validation:

   a. Bench-top stability (short-term stability of fentanyl in matrix at room temperature);

   b. Dilution integrity evaluation;

   c. Standard Operating Procedures (SOPs) that were employed during subject sample analysis including those dealing with sample repeats and analytical procedure;

2. You have only submitted the 90% confidence intervals for Ln AUCt, LnAUCinf and LnCmax in the integrated study report, but didn't provide a comprehensive pharmacokinetic and statistical report for this study. Please provide the following information in a tabulated format: 1) mean, standard deviation, coefficient of variation (%CV) and Test/Reference ratios for all derived pharmacokinetic parameters (AUCt, AUCinf, Cmax, Tmax, T1/2 and Kel) and for plasma concentration at each scheduled sampling time, 2) SAS Analyses of Variance report.

3. Please provide the dissolution methods (apparatus, rotation speed, volume and temperature of the media) that were used in your multimedia dissolution testing. For the dissolution data, please provide raw data for individual dosage units, including range values (low, high), CV percentage, or f2 values. In addition, please provide your proposed dissolution method and specification for quality control and stability testing of your product.

4. Please clarify if your multimedia dissolution data were presented as percentage of total delivered dose (µg/hr*24 hr*3. If so, please resubmit those data presented as percentage of labeled amount per patch.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 77-449

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

May 3, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCY AMENDMENT

N/AB

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
BIOEQUIVALENCY AMENDMENT - RESPONSE TO APRIL 12, 2006 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated April 12, 2006. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Deficiencies

1. a-c Please note that your comments have been addressed by (b) (4), the bioanalytical laboratory which conducted the bioanalytical method validation. (b) (4)'s responses are provided as **Attachment 2**.

2. Please find enclosed, as **Attachment 3**, the requested pharmacokinetic and statistical information in a tabulated format.

3. The dissolution parameters that were used in the multimedia dissolution testing are listed below:

Apparatus:	Apparatus 6 (cylinders)
Rotation Speed:	50 rpm
Volume:	500 mL for 25 µg/hr and 50 µg/hr 900 mL for 75 µg/hr and 100 µg/hr
Temperature:	32.0 ± 0.5°C

Please refer to **Attachment 4** for the tabulated dissolution data presented as both a percentage of total dose released (TDR) and label claim (LC).

Please find enclosed, as **Attachment 5**, the proposed dissolution method (STP Number: 428, Revision 2). Please note that this is the same dissolution method that was supplied in the original ANDA.

Please find enclosed, as part of **Attachment 5**, the current drug product specifications which include the proposed specifications for drug release. Please note that the provided specifications are identical to those submitted in our February 24, 2006 minor amendment.

4. Please note that the multimedia dissolution data was presented as a percentage of total dose release (TDR). Please refer to **Attachment 4** for the tabulated dissolution data presented as both a percentage of total dose released (TDR) and label claim (LC).

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

ANDA 77-449

MAY 19 2006

TEVA Pharmaceuticals, USA
1090 Horsham Road
PO Box 1090
North Wales, PA 19454
Attn: Philip Erickson

Dear Sir:

This letter is in reference to your abbreviated new drug application dated December 17, 2004 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr.

FDA is investigating reports of death and other serious side effects from overdoses of fentanyl in patients using fentanyl transdermal patches. In order to assess the potential contribution of pharmacokinetics in causing serious adverse events, we are reviewing the available individual pharmacokinetic data for fentanyl transdermal systems. We are specifically concerned about consistency of dosing with transdermal fentanyl patches because there is a narrow margin between the serum concentrations of fentanyl that provide the desired analgesic effect and the concentrations that may be associated with serious toxicity.

Please review all human fentanyl blood/serum concentration data in your clinical/biopharmaceutics database associated with use of any transdermal fentanyl product (i.e., your own or another manufacturer's product). Please identify all individual subjects or patients with any fentanyl concentrations above the following fentanyl plasma concentration threshold for each patch strength:

Patch Delivery Rate (mcg/hr)	Fentanyl Plasma Concentration Threshold ng/mL
12	1.8
25	4.2
50	5.1
100	7.5

Please include individuals with any or all of their data points exceeding the above respective threshold.

For all such individuals, please provide the following information (as available):

- Identify the fentanyl transdermal product that produced the high concentrations.
- Complete plasma-time concentration graph

- The results of any repeat, confirmatory assays performed on the same samples that resulted in high concentrations.
- Please submit any information pertaining to measurements of the fentanyl metabolite, norfentanyl in these patients.
- Identify the site of the fentanyl system application on the skin and also identify the site from which the blood sample with high fentanyl plasma concentration was drawn.
- Provide all available information regarding any adverse events potentially associated with high fentanyl concentrations in these studies.
- Provide all available information regarding the following parameters at the time of peaks in fentanyl concentrations: time of day, time since patch was applied, patient/subject activity, ambient temperature, vital signs, symptoms, etc.
- If the reported data are from multiple-dose studies, how many patches were applied before the high serum concentration was observed? How many apparent "peaks" were observed? Were the patches applied to the same site or rotating sites? What was the frequency of patch application? If any patches detached, were they replaced? How soon after the previous application was a patch replaced?

Please submit the following information from the studies wherein you found patients/subjects with high fentanyl plasma concentration or apparent spikes in fentanyl plasma concentrations [greater than 2 standard deviations from the mean]:

- Final study report
- Protocol
- Patient/subject demographics
- Fentanyl concentration-time individual data-submit data as SAS transport files.
- Fentanyl assay and validation/quality control reports

In addition, please provide the following information regarding your database for studies that show no fentanyl concentrations above the expected therapeutic range:

- Number of studies with no excess concentrations (either sustain or as a spike)
- Identify the fentanyl transdermal product(s) studied
- Frequency and timing of fentanyl blood concentration measurements
- Total number of subjects/patients in studies with no high fentanyl concentrations
- Number of fentanyl transdermal systems applied in each of these studies and duration of each application period

Please submit this information to the FDA within 4 weeks from the date of this letter.

If you have any questions, please contact Ted Palat at (301)594-0338. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Robert Lumpkin for
5/19/2006

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #77-449
Division File
Field copy
HFD-600/G.Buehler
HFD-610/R.West
HFD-600/D.Hixon

ENDORSEMENTS:

HFD-600/D.Hixon/
HFD-617/T.Palat/

V:\FIRMSNZ\TEVA\LTRS&REV\Fentanyl sponsor letter (4).doc
F/T by: CK

Information Request Letter

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

June 5, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N-AF

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
LABELING AMENDMENT - RESPONSE TO SEPTEMBER 20, 2005 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated September 20, 2005. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Labeling Deficiencies:

1. BLISTER – 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   a. Please find enclosed, as **Attachment 2**, diagrams of the proposed blister package configurations. Please note that a single fentanyl transdermal unit is placed into a (b) (4) tray and covered by the (b) (4) pouchstock which is heat-sealed onto the tray. Please find enclosed, 10 packaged placebo samples for each patch size which should aid in providing an understanding regarding our blister package configurations. Please note that similar samples were provided via our August 11, 2005 response to a request for samples. Please find enclosed, as **Attachment 3**, a disk containing draft copies (both PDF and Word) of our proposed blister labeling for each strength. Please note that reference to the lot number and expiry have not been incorporated into the blister labeling as this information will be laser etched onto the blister itself.

   b. Please find enclosed, as **Attachment 4**, a sample of the innovator's pouch labeling and a representative side by side comparison between our blister labeling and the information appearing on the innovator's pouch. The comparison shows that our proposed labeling contains similar information to that which appears on the innovator's pouch.

2. UNIT BACKING

Please note that the backing will contain the established name and strength in a clearly legible manner. A sample of the backing is provided for your review. Please note that although the provided sample does not include the product name and strength, it does incorporate the inks which may be used. Information which demonstrates that the inks do not migrate through the backing is enclosed as **Attachment 5**. Please note that the inks, manufactured by (b) (4), are the same inks approved for use in AVEVA's NDA #19-983 for Prostep (Nicotine Transdermal System). Additionally, please note that the product name and strength will be repeated in such a way as to ensure that each patch will contain the full product name and strength.

3. CARTON – 5 systems

a. As requested, the designation for hour has been changed from "h" to "hr".

b. We have included the text "(b) (4)" in a prominent manner for all strengths.

c. Reference to the "(b) (4)" has been removed from the listing of the inactive ingredients as these materials are not a part of the formulation of the drug product.

d. As requested, we have enclosed the statement "(b) (4)" to enhance the prominence in accord with the innovator's labeling.

4. INSERT

a. GENERAL

i. As requested, the designation for hour has been changed from "h" to "hr" throughout the insert.

ii. In conjunction with the fact that we are not seeking the approval of pediatric information protected by the exclusivity until its expiration and the fact that FDA regards all pediatric information subject to the exclusivity as safety information, we have retained all pediatric information in our labeling.

iii. Our labeling has been revised in accord with innovator's labeling last approved on February 4, 2005.

iv. As requested, we have removed and/or replaced text such that it is specific to our drug product (matrix system).

v. The term "fentanyl transdermal system" has been used throughout the text in place of "Duragesic" or "Duragesic patch".

b. PATIENT INFORMATION LEAFLET

i. The comments under GENERAL have been applied to the patient information leaflet, as applicable.

ii. In accord with the reference listed drug, one patient information leaflet will be provided inside each carton.

In accord with the changes noted above, please find enclosed, as **Attachment 3**, a disk containing draft carton labels (Iss. 10/2005) for each strength, along with a comparison to that of our last submitted carton labels (Iss. 11/2004). Also provided on the disk are electronic versions of the draft package insert and patient information leaflet (Iss. 10/2005), in both Word and PDF formats. Additionally, PDF comparison files comparing the revised package insert and patient information leaflet to the last submitted (Iss. 11/2004) are also provided for ease of your review.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

ORIG AMENDMENT
N- AA

June 13, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RESPONSE TO MAY 19, 2006
REQUEST FOR INFORMATION

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
RESPONSE TO MAY 19, 2006 REQUEST FOR INFORMATION

Dear Mr. Buehler:

We submit herewith information to the above-referenced, pending Abbreviated New Drug Application in response to a letter from your office dated May 19, 2006. For ease of review a copy of your letter is provided herein. Specifically, you had requested information pertaining to human fentanyl blood/serum concentration data in order to assess the potential contribution of pharmacokinetics in causing serious adverse events.

Please note that we have reviewed the data (both test and reference) from the study included in ANDA #77-449 as well as another study submitted to the Canadian regulatory authorities. The review of the data shows that there are no individual subjects with fentanyl concentrations above the fentanyl plasma concentration threshold stipulated in your May 19, 2006 correspondence. Additionally, no studies conducted by Teva have found plasma concentrations that yielded high fentanyl plasma concentrations or spikes (greater than 2 standard deviations from the mean).

We have conducted two studies with no aberrantly high plasma concentrations in either study. In each study we studied the 25 mcg/hr patch in a single dose. In each study, one 25 mcg/hr patch was applied for 72 hours and then removed. In one study (submitted in ANDA #77-449) 36 healthy normal volunteers were dosed using a Naltrexone rescue, while in the other study (submitted to the Canadian regulatory authorities) 28 were dosed using a Naltrexone block. Both studies were 2-way crossover BE studies comparing test to reference product PK profiles.

The blood draw schedule for the 36 subject study was as follows: 0, 3, 6, 12, 24, 36, 48, 60, 72, 74, 76, 78, 80, 82, 90, 96, 102, 108, 120, 132, and 144 hours post dose, for a total of 21 blood draws.

The blood draw schedule for the 28 subject study was as follows: 0, 3, 6, 9, 12, 24, 30, 36, 42, 48, 54, 60, 66, 72, 75, 79, 83, 90, 96, 102, 108, 120, 132, and 144 hours post dose, for a total of 24 blood draws.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned letter. If there are any additional questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

M E M O R A N D U M

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

DATE: AUG 2 1 2006

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Citizen Petitions Submitted Regarding Fentanyl Transdermal

TO: The ANDA Files for Fentanyl Transdermal:

ANDA 77-051 - Lavipharm Laboratories, Inc
ANDA [redacted] (b) (4)
ANDA [redacted]
ANDA 77-775 - Hisamitsu Pharmaceuticals
ANDA 77-154 - Tyco Healthcare
ANDA 77-449 - Teva Pharmaceuticals
ANDA 76-709 - Watson Pharmaceuticals
ANDA [redacted] (b) (4)
ANDA 77-062 - Abrika Pharmaceuticals

Background:

Mylan submitted two citizen petitions regarding Fentanyl Transdermal Systems. Mylan's petition 2006P-0123/CP1 submitted on March 17, 2006, requests that the Food and Drug Administration (FDA or Agency) require that all applicants for fentanyl transdermal systems conduct a study to determine the effect of using overlays with their respective patches and include in the approved labeling appropriate information on the type of overlay(s) that may be used with the fentanyl patch. Mylan submitted supplements on March 21, 2006 and on May 25, 2006. A comment was also submitted by Pricara on July 21, 2006. Pricara is a unit of Ortho McNeil, the parent for Alza, the NDA holder for the listed drug, Duragesic. Pricara concurs with Mylan's request that the FDA require that applicants for fentanyl transdermal systems conduct a

6.1

study to determine the effect of use of an overlay with their respective patches. They indicate that they have completed such a study and are currently analyzing the findings of the trial. No data regarding this study have been (b) (4) and the currently approved Duragesic labeling makes no reference to overlay use. Mylan also indicates in its petition that they are currently undertaking a study to support the safe and appropriate use of an overlay.

Mylan's second petition 2006P-0290/CP1, submitted on July 24, 2006, requests that FDA determine the necessity for a Risk Management Program (RMP) for fentanyl transdermal drug products. This petition further requests that, if the Agency determines that an RMP is necessary, the Agency develop and adopt a single, unified RMP for all transdermal fentanyl products, based on input provided by all sponsors of approved marketing applications for transdermal fentanyl drug products. Currently the Division of Analgesics, Anesthetics and Rheumatology Drug Products is considering an RMP for fentanyl transdermal systems but none has been approved.

Effect of Petitions on ANDA Approvals

These two petitions do not currently raise issues that go to the underlying approvability of any pending ANDAs. Thus, although FDA intends to consider the issues raised in and answer these petitions, FDA need not resolve the issues they raise prior to approving additional ANDAs for fentanyl transdermal systems.

Generally, to obtain approval, an ANDA must establish, among other things, that it has the "same labeling" as the listed drug it references. Specifically, with regard to the labeling, an ANDA applicant must submit "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for [a listed drug]" 21 U.S.C. 355(j)(2)(A)(i) and must establish that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug [referenced] . . . except for changes required because of differences approved under a [suitability petition] or because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. 355(j)(2)(A)(v).

As noted above, in the first petition, Mylan suggests that ANDA applicants should be required to study their product when used with an appropriate overlay. However, the reference listed drug, Duragesic, is not currently approved for use with an overlay and its labeling is silent on the effects of overlay use. Under these circumstances, the existence or non-existence of an overlay study in an ANDA does not correspond to either the approved conditions of use or the approved labeling of the Duragesic NDA and, thus, does not correspond to any of the ANDA approval requirements. Accordingly, resolution of the issues raised in Mylan's petition is not an essential prerequisite to approval of pending ANDAs. If Duragesic subsequently obtains approval for use with an overlay, FDA will consider what, if any, additional studies may be required of pending and approved ANDAs referencing Duragesic at that time.

Mylan's second petition regarding risk management plans also does not raise issues that go to FDA's ability to approve additional ANDAs for fentanyl transdermal systems. As noted above, this petition requests that FDA determine whether an RMP is necessary for fentanyl transdermal drug products, and if the Agency determines that an RMP is necessary, requests that the Agency develop and adopt a single, unified RMP for all transdermal fentanyl products, based on input provided by all sponsors of approved marketing applications for transdermal fentanyl drug products. FDA is currently considering whether to request that fentanyl transdermal products adopt an RMP to assure their safe and effective use. However, unless and until such an RMP is approved for Duragesic (or Duragesic is subject to withdrawal proceedings for failure to adopt an RMP), FDA cannot withhold approval of an ANDA for failure to include such a program. Nor must FDA withhold ANDA approval while it decides the procedure for determining whether an RMP for fentanyl transdermal systems will be necessary and, if necessary, its contents. If Duragesic adopts an RMP, ANDAs referencing Duragesic will be expected to adopt the required elements of the RMP adopted. However, in the interim, while Duragesic continues to be marketed without an RMP, ANDAs referencing Duragesic can also be approved and marketed without adopting an RMP.

Under 21 U.S.C. 355(j)(4) of the Act, FDA is required to approve an ANDA unless it fails to meet the requirements for approval. ANDAs for a fentanyl transdermal system that meet the requirements for approval must be approved, even if the Agency believes the conditions of approval or the labeling for the listed drug they reference may soon change. Both of Mylan's petitions recommend certain changes in labeling and/or conditions of approval for Duragesic, which will require changes in pending and approved ANDAs only if they are adopted for the RLD. Unless and until those changes are made for Duragesic, Mylan's two fentanyl petitions do not raise issues that go to the underlying approvability of any pending ANDAs referencing Duragesic and the issues they raise need not be resolved prior to additional ANDA approvals.

q:\issues\fentanyl\fentanylmemo.doc

cc: OGD Control #06-0440
G. Buehler/R. West/L. Yu/C. Parise/D. Read/D. Hixon/D. Hare/F. Holcombe/HFD-600
P. Rickman/HFD-615
M. Shimer/HFD-613
R. Patel/HFD-620
F. Fang/HFD-640
V. Sayeed/HFD-630
D. Conner/HFD-650
N. Boocker/N. Kim/HFD-7

Drafted by C. Parise 8/16/06
Edited by K. Dettelbach and S. Vaid 8/17/06

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Debra Catterson PROJECT MANAGER: (301) 827-7301

Dear Sir:

This facsimile is a request for information from the Clinical Review Team, regarding your ANDA 77-449 for Fentanyl Transdermal System, 25mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr.

The information request is presented on the attached 5 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 77-449

To: **Teva Pharmaceuticals USA**

Drug: **Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr**

From: **Sarah Ho, Pharm.D.**
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, M.D.
Associate Director of Medical Affairs
Office of Generic Drugs

Date: **November 17, 2006**

Re: **Request for Information**

In order to facilitate the review of skin irritation, sensitization and adhesion data for your application for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr (ANDA 77-449), please provide the following information:

A. Please clarify the name(s) of the CRO, if any, for the skin irritation, sensitization and adhesion studies (Protocol #770-0407-01 and #770-0407-03) and the pharmacokinetic bioequivalence study (Protocol #770-0407-02).
B. Please provide copies of CRFs from a sample selection of 20 subjects from each of the two skin irritation, sensitization and adhesion studies (Protocol #770-0407-01 and #770-0407-03).
C. The CRFs for your pharmacokinetic bioequivalence study (Protocol #770-0407-02) do not provide for the documentation of adhesion and irritation scores. Please clarify how these data were documented and provide copies of the documentation.
D. Please submit skin irritation, sensitization and adhesion information in electronic format for these studies (Protocol #770-0407-01 and #770-0407-03) and your pharmacokinetic bioequivalence study (Protocol #770-0407-02):

    1. Study data should be submitted to the OGD in electronic format.
        a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included.
        b. Please provide a "define.pdf" document with detailed description of codes that you use for each variable in each of the SAS datasets (for example, 0=yes, 1=no for analysis population). Please refer to http://www.fda.gov/cder/guidance/2353fnl.pdf regarding “define.pdf”.

c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.

2. For each study, a summary dataset containing the following line listings should be provided for each individual test article per subject, if applicable:

   a. Center
   b. Subject number
   c. Test article (i.e., test, reference, placebo, positive controls, negative control)
   d. Race
   e. Gender
   f. Age
   g. Patch application site
   h. Test article discontinued (yes/no)
   i. Reason for discontinuation of test article
   j. Time from first application to discontinuation of test article
   k. PP population for irritation analysis (yes/no), reason for exclusion
   l. PP population for sensitization analysis (yes/no), reason for exclusion
   m. PP population for adhesion analysis (yes/no), reason for exclusion (no need to analyze adhesion of controls)

   Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your studies and/or it may not contain information applicable to your studies.

3. For the Irritation Analysis, please provide a separate line listing for each individual test article per subject, per each visit (if data exist):

   a. Subject number
   b. Test article (i.e., placebo, positive control, negative control)
   c. Test article application site
   d. Visit number
   e. Date of visit
   f. Days from baseline
   g. Application number
   h. Application day (specify day of week, e.g., Monday, Wednesday or Friday)
   i. Application date
   j. Application time
   k. Removal date (For each individual application)
   l. Removal time (For each individual application)
   m. Time from test article application to removal or detachment
   n. PP population inclusion (yes/no)
   o. Reason for exclusion from PP population for irritation analysis
   p. Irritation scores (numeric)
   q. Other effects scores (letter scores)

r. Adverse events reported during this visit (yes/no)
s. Reason for discontinuation
t. Test article moved or discontinued for unacceptable irritation during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your irritation analysis and/or it may not contain information applicable to your irritation analysis.

4. For the Adhesion Analysis, please provide a separate line listing for each test article application per subject, per each visit (if data exist):

   a. Subject number
   b. Test article (i.e., test, reference, placebo, positive control, negative control)
   c. Test article application site
   d. Visit number
   e. Date of visit
   f. Days from baseline
   g. Application number
   h. Application day (specify day of week, e.g., Monday, Wednesday or Friday)
   i. Application date
   j. Application time
   k. Removal date for each individual application
   l. Removal time for each individual application
   m. Time from patch application to removal or detachment
   n. PP population inclusion (yes/no)
   o. Reason for exclusion from PP population for adhesion analysis
   p. Adhesion scores
   q. Was the patch reinforced with tape or overlay (yes/no)
   r. If patch was reinforced, time from patch application to reinforcement

   Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your adhesion analysis and/or it may not contain information applicable to your adhesion analysis.

5. For the Sensitization Analysis, please provide a separate line listing per subject, per each visit in the induction and challenge periods (if data exist):

   a. Subject number
   b. Test article (i.e., placebo, positive control, negative control)
   c. Test article application site
   d. Visit number
   e. Date of visit
   f. Days from baseline
   g. Application day (specify day of week, e.g., Monday, Wednesday or Friday)
   h. Application date
   i. Application time

j. Removal date
k. Removal time
l. Time from test article application to removal or detachment
m. PP population inclusion (yes/no)
n. Reason for exclusion from PP population for sensitization analysis
o. Irritation/Sensitization numeric scores for induction and challenge periods
p. Letter scores for induction and challenge periods
q. Potentially sensitized (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your sensitization analysis and/or it may not contain information applicable to your sensitization analysis.

6. Please provide separate datasets for each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

Table 1: Example of a summary dataset for each individual test article per subject

subj	center	race	gender	age	treat	site	PPirr	PPirr_rs	PPad	PPad_rs	PPsen	PPsen_rs	mv	mv_n	dis	Dis_rs	AE
1	001				A	R	Yes		Yes		Yes		No		No		
1	001				C	L	Yes		Yes		Yes		Yes	1	No		
1	001				D	M	No	B	YES		No	B	Yes	1	No		
2	001				A	M	No	A	No	A	No	A	Yes	2	Yes	A	Yes
2	001				C	L	Yes		Yes		Yes		No		No		
2	001				D	R	No		No		No		No		No		

subj: subject number
center: center
race: race
gen: gender/sex
age: age
treat: treatment or test article, e.g. article A, B, C, D or article A, C, D
site: patch application site, e.g., R=right, L=left, M=middle, etc.
PPirr: PP population for irritation analysis (yes/no)
PPirr_rs: Reason for exclusion from PP population for irritation analysis,
e.g., A=discontinue early due to AE B=patch fell off, C=subject moved out of the area, etc.
PPad: PP population for adhesion analysis (yes/no)
PPad_rs: Reason for exclusion from PP population for adhesion analysis,
e.g., A=discontinue early due to AE, C=subject moved out of the area, etc.
PPsen: PP population for sensitization analysis (yes/no)
PPsen_rs: Reason for exclusion from PP population for sensitization analysis,
e.g., A=discontinue early due to AE, B=patch fell off, C=subject moved out of the area, etc.
mv: test article moved (yes/no)
mv_n: number of times test article was moved due to irritation score ≥3, e.g., 1, 2
dis: discontinuation of the test article (yes/no)

dis_rs: reason for test article discontinuation, e.g., A=irritation, etc
AE: occurrence of adverse events for this treatment arm (yes/no)

Table 2: Example of a line listing for each individual test article per visit per subject

Subj	Treat	Site	Visit	Date	Baseline	Ind	Scr_date	Exc_rs	Ind_n1	Ind_c1	Ind_n2	Ind_c2	Ind_n3	Ind_c3	AE	Mv_dis	Mvdis_rs	Mvdis_da	.
1	A	L	1																
1	A	L	2																
1	A	L	3																
1	A	L	4																
1	A	L	5																
1	A	L	6																
.	.	.	.																

Subj: subject number
Treat: treatment
Site: patch application site, e.g., R=right, L=left, M=middle, etc.
Visit: visit number
Date: visit date
Baseline: day from baseline
Ind: application number
Scr_date: score day
Exc_rs: reason for exclusion from analysis, e.g., A=subject did not show for appointment, schedule conflicts, protocol/exclusion criteria violation, B=patch detached for more than 24 hours, etc.
Ind_n1: numeric irritation score in the first site
Ind_c1: character irritation score in the first site
Ind_n2: numeric irritation score in the second site (if application site moved due to excessive irritation)
Ind_c2: character irritation score in the second site
Ind_n3: numeric irritation score in the third site
Ind_c3: character irritation score in the third site
AE: occurrence of adverse events reported during this visit (yes/no)
Mv_dis: test article moved or discontinued
Mvdis_rs: reason for test article moved or discontinued
Mvdis_dt: date test article was moved or discontinued

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

/s/

Dena Hixon

11/17/2006 04:46:51 PM

MEMORANDUM

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

DATE: September 7, 2006

TO: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs (HFD-600)

FROM: Mark J. Seaton, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering ANDA 77-449, Fentanyl Transdermal System, 25, 50, 75, and 100 µg/h, sponsored by Teva Pharmaceuticals.

At the request of HFD-600, the Division of Scientific Investigations conducted an audit of the following skin sensitization studies:

> Protocol 770-0407-01 - A 21-Day Cumulative Irritation Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Healthy Adult Subjects.

This was a single-center, single blind (skin evaluator was blinded), multiple-application, cumulative irritation study of a placebo transdermal delivery system (TDS) performed by PRACS Dermatology, LLC (San Diego, CA). Healthy adult subjects had one placebo patch, one negative control patch (0.9% sodium chloride) and two positive control patches (0.02% and 0.04% sodium lauryl sulfate) applied daily to the upper back for 21 consecutive days. Dermal response was rated using a scoring scale.

> Protocol 770-0407-03 - Sensitization Study of a Placebo (Drug Free) Fentanyl Transdermal Delivery System (TDS) in Adult Subjects.

This was a single-center, single blind (skin evaluator was blinded), multiple-application, repeat insult patch test of

the placebo transdermal system (TDS), performed by PRACS Institute, Ltd. (Fargo, ND). Healthy adult male and female subjects had one placebo TDS applied three times a week for a total of 9 applications (induction phase) and one TDS applied following a two week rest period (challenge phase). Dermal reactions were rated using a scoring scale and a scale describing features indicative of irritation (e.g., edema).

Following inspection at PRACS Institute, Ltd. (Fargo, ND) no form FDA 483 was issued. Following inspection at PRACS Dermatology, LLC (San Diego, CA), a one-item form FDA 483 was issued. The objectionable finding and our evaluation is provided below.

> The following Form FDA 483 observation pertains to the conduct of protocol 770-0407-01:
>
> **The protocol was not followed in that subjects #332 and #333 did not receive all required patches throughout the study. Deviation reports in case histories and the Study Report indicate that the positive and negative control patches were dropped on 7/28/04 and 7/27/04, respectively, due to tape irritation. The subjects were not discontinued from the study and their respective irritation scores were reported for all time points and patches in the Study Report dated 9/14/04.**

According to the Study Director, PRACS Dermatology, LLC (San Diego, CA) normally reports all data, including data from residual irritation, to the sponsor, and allows the sponsor to decide how the data will be reported to the FDA. Our review of the information reported to the FDA (ANDA 77-449, Section VI.7.b, pages 2596 - 2599) revealed that the residual irritation data for subjects #332 and #333 were included in the final statistical analyses for this study.

Conclusion:

DSI concludes that the accuracy of the statistical analyses of the irritation data cannot be assured for protocol 770-0407-01. The OGD reviewer should be aware that subjects #332 and 333 did not receive control patches B, C and D (0.9% sodium chloride, 0.02%, and 0.04% sodium lauryl sulfate, respectively) from Application Day 9-21 and Application Day 8-21, respectively. However, irritation

scores for all study time points (Application Days 1-21) were recorded for those subjects, and were included in the statistical analyses.

After you have reviewed this transmittal memo, please append it to the original ANDA submissions.

Mark J. Seaton, Ph.D.

Final Classifications:

PRACS Institute, Ltd. (Fargo, ND)	**NAI**
PRACS Dermatology, LLC (San Diego, CA)	**VAI**

cc:
HFD-45/RF
HFD-48/Seaton/Himaya/CF
HFD-600/Catterson/Hixon/ANDA 77-449
HFR-CE300/Holaday
HFR-PA2535/Hall
Draft: MJS 9/7/06
Edit: MKY 9/11/06
DSI: 5640; O:\BE\EIRCOVER\77449tev.fen.doc
FACTS: 677042

Att:

1. FDA-483: **PRACS Dermatology, LLC (San Diego, CA)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, California 92612-2500 949-608-2900	2/16,17&21/06
	FEI NUMBER 3004427970

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert A. Harper, Ph.D., Director, Clinical Research

FIRM NAME	STREET ADDRESS
PRACS Institute, Ltd.	15222 Avenue of Science, Suite B
CITY, STATE AND ZIP CODE San Diego, CA 92128	TYPE OF ESTABLISHMENT INSPECTED Biopharmaceutics Clinical Facility

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

The following observation pertains to the establishment's conduct of a clinical trial (#04-128, 770-0407-01). The observation is based on the review of records including case histories for 12 subjects from a total of 37 subjects enrolled in the study at this site.

1.

The protocol was not followed in that subjects #332 & #333 did not receive all required patches throughout the study. Deviation reports in case histories and the Study Report indicate that the positive and negative control patches were dropped on 7/28/04 & 7/27/04 respectively due to tape irritation. The subjects were not discontinued from the study and their respective irritation scores were reported for all time points and patches in the Study Report, dated 9/14/04.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Allen F. Hall	Allen F. Hall, CSO	2/21/06

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

/s/

Jacqueline OShaughnessy
12/26/2006 11:25:02 AM
PHARMACOLOGIST
Paper copy signed by Drs. Viswanathan and Seaton.

tox consult sent 4/4/07 BTR

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

January 3, 2007

ORIGINAL

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
AM

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
MINOR AMENDMENT - RESPONSE TO AUGUST 9, 2006 REVIEW LETTER &
NOTIFICATION OF THIRD PARTY SUBMISSION

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated August 9, 2006. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

A. Deficiencies

1. With regard to the request for the addition of (b) (4) to the finished product release and stability specifications, we propose the following:

Test	Proposed Release & Stability Specification
(b) (4)	

Please find enclosed, as **Attachment 2**, updated product specification sheets for each strength of finished product. The data used to establish the finished product specification for (b) (4) are also provided. Additionally, we are providing the standard testing procedure (b) (4) which corresponds to the finished product test for (b) (4).

2. Please note that your comments have been addressed by (b) (4) (b) (4), the manufacturer of the (b) (4) provided the toxicology information previously submitted to this ANDA on behalf of TEVA Pharmaceuticals USA. Their response is provided as **Attachment 3**.

RECEIVED
JAN 0 4 2007
OGD / CDER

Please note that in order to address concerns regarding the [redacted] contained in our product, the manufacturer [redacted] will submit toxicology information (as a controlled document) directly to the Agency for TEVA's ANDA. TEVA hereby grants [redacted] the authority to submit such data as a confidential submission to ANDA #77-449. Additionally, we have included (**Attachment 4**) a toxicological profile for the [redacted] products produced by [redacted].

Please note that manufacturers of the aforementioned adhesives do not perform toxicological studies on every adhesive as the adhesives are often within the same chemical class and differ only in molecular weight. Testing is often limited to polymeric substances of lower molecular weight, as it is generally recognized that mammalian toxicity decreases with increasing molecular weight because the polymers with higher molecular weight are less dermally active. Therefore, the toxicological studies provided by [redacted] as well as those to be provided by [redacted] are intended to represent a "worst case" evaluation of a chemical class of polymers and the results are applicable to those of higher molecular weights within the same chemical class of polymers.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

ORIG AMENDMENT
N/AB

January 16, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCE
TELEPHONE AMENDMENT

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
BIOEQUIVALENCE TELEPHONE AMENDMENT–RESPONSE TO JANUARY 5, 2007
TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a telephone contact with Keri Suh of the Agency's Division of Bioequivalence on January 5, 2007. Specifically, clarification was requested regarding the multi media dissolution data supplied in the original ANDA and that which was submitted via our May 3, 2006 bioequivalency amendment.

Please note that the multi media dissolution datasets were incorrectly labeled in the report submitted in the original ANDA (pgs. 2377-2386). Please find enclosed, an updated report which correctly identifies the dissolution datasets and also presents the data as both a percentage of total dose released (TDR) and label claim (LC). Please note that although it may appear that there are slight differences (± 1%) in some of the values between the updated report (contained herein) and the data tables submitted via our May 3, 2006 bioequivalency amendment, the difference is solely due to rounding and does not constitute a significant difference in value.

This information is submitted toward the review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosure

RECEIVED
JAN 17 2007
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
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Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

January 31, 2007

ORIG AMENDMENT
AB

BIOEQUIVALENCY AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIGINAL

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
BIOEQUIVALENCY AMENDMENT - RESPONSE TO NOVEMBER 17, 2006 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated November 17, 2006. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Deficiencies

A. Please note that information regarding the names and sites of the CROs for the skin irritation, sensitization and adhesion studies and the pharmacokinetic bioequivalence study was provided in the original ANDA (pgs. 3-4 and 121). Please note that each study was conducted at a single center. For ease of review, the information is provided below:

Skin Irritation Study (Protocol #770-0407-01)*

PRACS Institute, Ltd.
15222-B Avenue of Science
San Diego, CA 92128

Skin Sensitization Study (Protocol #770-0407-03)*

PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58106

RECEIVED
FEB 01 2007
OGD / CDER

* The secondary objective of these studies was to assess the adhesion of the AVEVA placebo 25 µg/hr fentanyl TDS prior to removal at every visit.

Pharmacokinetic Bioequivalence Study (Protocol #770-0407-02)

Clinical Facility:
NOVUM Pharmaceutical Research Services
5900 Penn Avenue
Pittsburgh, PA 15206

Analytical Facility:
(b) (4)

B. Please find enclosed, as **Attachment 2,** a disc containing copies of CRFs from a sample selection of 20 subjects from each of the skin irritation, sensitization and adhesion studies (Protocol #770-0407-01 and #770-0407-03).

C. Please note that the adhesion and irritation scores for the pharmacokinetic bioequivalence study (Protocol #770-0407-02) were documented in logs that were maintained separately from the individual CRFs. The adhesion and irritation logs are included on the disc enclosed as **Attachment 3**.

D. As requested, the skin irritation, sensitization and adhesion information for the studies performed, are provided in electronic format. Please refer to the table below for clarification regarding the various discs provided.

Reference	Corresponding Protocol #	Study Number	Corresponding Disc
Sample CRFs	770-0407-01 & 770-0407-03	PRACS 04-128 & PRACS R04-0601	Attachment 2
Pharmacokinetic Bioequivalence Study	770-0407-02	NOVUM 10471601	Attachment 3
Irritation Study	770-0407-01	PRACS 04-128	Attachment 4
Sensitization Study	770-0407-03	PRACS R04-0601	Attachment 5

1. The study data provided herein is submitted in electronic format. Please note that the information provided has been compiled based on the information available from the study data files. As indicated in your correspondence, the exact construct of the various data files varies from study to study depending on the individual study design and objectives of the study.

   a. The discs containing SAS datasets include a list of file names with a simple description of the content of each file. The list may be found in the define.pdf.

   b. The discs containing SAS datasets include a "define.pdf" document which provides descriptions of codes/variables contained within the SAS datasets.

   c. The SAS transport files provided on the enclosed discs include .xpt as the file extension and are not compressed.

2. Please refer to the discs for a summary dataset for each individual test article per subject who participated in the study.

3. Please refer to the discs for separate line listings for the irritation analysis.

4. Please refer to the discs for separate line listings for the adhesion analysis.

5. Please refer to the discs for separate line listings for the sensitization analysis.

6. Please note that separate datasets, which include the applicable variables, are provided for each study.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Teva Pharmaceuticals TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Keri Suh PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 21, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached eleven pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. We agree with your proposed dissolution method. However, your proposed dissolution specification is not acceptable. Please provide a statement of your acceptance of the following dissolution method and specification:

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/hr strengths) and 900 ml (for the 75 and 100 µg/hr strengths)of Phosphate buffer pH 6.8 at 32°C±0.5°, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours:
   24 hours: %

   (Please note that the specifications are presented as percentage of **labeled amounts** per patch)

2. Your formulation is not acceptable pending a satisfactory response to the deficiencies from the FDA Pharmacology review regarding the toxicology information provided for the adhesives.

The following comments are for your future applications:

1. Please conduct separate bench-top stability and freeze/thaw stability study, and conduct the dilution integrity study in the pre-study bioanalytical method validation instead of in the actual sample assay.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file for all your future application. For the dissolution data, in addition to the mean dissolution data, please also provide raw data for individual dosage units, range values (low, high) and CV percentage.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 1. Summary of Comparative Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (units)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M %CV M %CV	M %CV Med M %CV Med	M %CV M %CV	M %CV M %CV	M %CV M %CV	M %CV M %CV	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M %CV M %CV	M %CV Med M %CV Med	M %CV M %CV	M %CV M %CV	M %CV M %CV	M %CV M %CV	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means*, Ratios of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				

* **Geometric Means Based on Least Squares Means of Ln-transformed Data**

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	@ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	**Conditions of Dissolution Testing:** Apparatus: Speed of Rotation: rpm Medium: Volume: mL Temperature: C± **Proposed Specification:**	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6A. Demographic Profile of Subjects Completing the Comparative Bioavailability Study (Fasting)

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD		
Range		
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 6B. Demographic Profile of Subjects Completing the Comparative Bioavailability Study (Fed)

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD		
Range		
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8A. Reanalysis of Study Samples (Fasting Study)

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of reanalyzed values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

Table 8B. Reanalysis of Study Samples (Fed Study)

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of reanalyzed values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[2]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

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/s/

Dale Conner

2/26/2007 09:47:18 AM

ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

April 3, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

UNSOLICITED CMC AMENDMENT

ORIG AMENDMENT
N-000-AA

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
UNSOLICITED CMC AMENDMENT – REVISION TO SPECIFICATION FOR (b) (4)

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced, pending Abbreviated New Drug Application. We hereby propose a revision to the drug product specification for (b) (4)

The drug product specification for (b) (4) was added as a result of FDA comment contained in a November 16, 2005 chemistry review letter. Please note that at the time of our response, product from ongoing stability studies (12 month) was tested and the data so generated were used to propose a specification. Acknowledging that limited data were available and upon subsequently evaluating additional stability data, we hereby propose the following revision to the (b) (4) specification.

Test	Current Release & Stability Specification	Proposed Release & Stability Specification
(b) (4)		

Please find enclosed, as **Attachment 1**, updated product specification sheets for each strength of finished product. Please note that the same product specification sheets were provided via our April 3, 2007 response to a February 26, 2007 review letter from the Division of Bioequivalence. The data used to establish the finished product specification for (b) (4) are also provided (**Attachment 2**). Please note that the provided (b) (4) data incorporates the same statistical evaluation of data that was used to establish specifications for other physical characteristics of the drug product. The physical characteristics of the product may be measured via a battery of tests such as (b) (4) being more indicative of the physical properties of the product. Please note that we hereby commit to evaluate the proposed specification following the first 10 commercial batches and possibly (b) (4) the specification, as appropriate.

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Additionally, the 24 month room temperature stability reports are enclosed herein (**Attachment 3**). Please note that these stability reports were also included in the above referenced Bioequivalence Amendment.

This information is submitted toward the continued review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/sc

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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April 16, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

UNSOLICITED CMC AMENDMENT

N/A A

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
UNSOLICITED CMC AMENDMENT – PROPOSED CHANGE IN BLISTER (b) (4)

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced, pending Abbreviated New Drug Application. We hereby propose a change to the (b) (4) used in the blister packaging of the drug product.

Please note that (b) (4). has discontinued production of (b) (4) which incorporated the (b) (4). This material was used to produce the (b) (4) blister package used in the packaging of the drug product. We hereby propose the use of (b) (4), which incorporates the (b) (4). Although, the (b) (4) products are similar with respect to their chemical composition and use in (b) (4) blister packaging, the materials are not considered equivalent with respect to their comparative physical properties. However, based on the knowledge of the physical properties of the materials and in conjunction with stability studies provided herein, the replacement film is deemed suitable for the protection of the drug product.

In support of the aforementioned change, we provide the following:

Attachment 1:

- DMF Letter of Authorization for (b) (4)
- DMF Letter of Authorization for

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Attachment 2:

- Technical Data Sheet for (b) (4)
- Technical Data Sheet for

Attachment 3:

- Technical Data Sheet for (b) (4) (for comparative purposes only)
- Technical Data Sheet for (b) (4) (for comparative purposes only)

Attachment 4:

- (b) (4) Classification Statement (US Pharmacopoeia Class VI)
- USP<661> Testing for (b) (4)
- USP<661> Testing for (for comparative purposes only)

Attachment 5:

- Specification Sheet for (b) (4)
- AVEVA Certificate of Analysis for (b) (4)
- Manufacturer's Certificate of Analysis for (b) (4)

Attachment 6:

- Accelerated and Room Temperature Stability Reports for the Drug Product (Smallest and Largest Patch Sizes – 25 µg/h and 100 µg/h)

Please note that the stability data provided herein was performed on drug product taken from the ongoing ANDA stability studies and repackaged into blister trays incorporating the proposed (b) (4) product. The repackaged drug product was at the proposed expiration date of 24 months at the time of repackaging and therefore represents a worst case scenario with regard to drug product performance in the blister trays. Please also note that no changes to the blister tray dimensions or any other blister package materials (ie. blister lidding) are being proposed. The packaging of the validation batches will incorporate the proposed (b) (4) product and we hereby commit to provide the stability reports via the Annual Report.

This information is provided for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
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ORIG AMENDMENT
N-AM1

April 24, 2007

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
TELEPHONE AMENDMENT – RESPONSE TO APRIL 13, 2007 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to an April 13, 2007 telephone request made by Shahnaz Read of the Office of Generic Drugs. Specifically, the call was in reference to our April 3, 2007 unsolicited CMC amendment which proposed a revision to the finished product specification for (b) (4) Ms. Read requested that we (b) (4) the proposed specification for (b) (4) in accord with a statistical evaluation based on three standard deviations from the mean of the previously supplied data.

Based on the requested statistical approach, we propose the following:

Test	Previously Proposed Release & Stability Specification	Currently Proposed Release & Stability Specification
	(b) (4)	

Please find enclosed herein, updated product specification sheets for each strength of finished product which incorporate the revised specification for (b) (4).

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the request presented in the aforementioned telephone contact. This information is submitted toward the review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

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APR 25 2007
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
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April 26, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N-AF

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
LABELING AMENDMENT - RESPONSE TO SEPTEMBER 25, 2006 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated September 25, 2006. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Labeling Deficiencies:

1. BLISTER – 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   Please find enclosed, as **Attachment 2**, a disk containing final print blister labeling (Iss. 2/2007) in both PDF and Word for each strength, along with a comparison to that of our last submitted blister labeling (Iss. 10/2005).

   a. In accord with your recommendation, we have relocated the information appearing on the Duragesic® pouch's back panel to our carton labeling, as our blister design does not permit the printing of information on both the front and back of the blister package. Please note that reference to the lot number and expiry have not been incorporated into the blister labeling as this information will be laser etched onto the blister itself.

   b. Please note that the prominence of the established name and strength has been increased by enlarging the font size.

   c. Please note that the strengths of drug product are differentiated by contrasting colors.

d. We have included the text "(b) (4) (b) (4)." in a prominent manner.

e. As requested, the controlled substance symbol has been relocated further away from the strength.

f. Please note that the inactive ingredients have been listed.

g. Please note that the blister labels contain the National Drug Code (NDC) number in a linear bar code format.

2. CARTON – 5 systems

Please find enclosed, as **Attachment 2**, a disk containing final print carton labeling (Iss. 9/2006) in both PDF and Word for each strength, along with a comparison to that of our last submitted carton labeling (Iss. 10/2005).

a. The comments under BLISTER have been applied to the carton, where applicable.

b. The text "(b) (4)," has been included on both panels 1 and 3 in a prominent manner similar to the innovator's carton.

3. UNIT BACKING

a. We note the Agency's acknowledgement regarding the inks used for printing.

b. Per request, samples of the unit backing are provided in **Attachment 3**. Please note that in order to ensure a clearly legible repeating pattern of the name and strength, we propose to list the active ingredient and strength only.

4. INSERT

In accord with the changes noted below, please find enclosed, as **Attachment 2**, a disk with electronic versions of the final print package insert and patient information leaflet (Iss. 3/2007) in both Word and PDF formats. Additionally, PDF comparison files comparing the revised package insert and patient information leaflet to the last submitted (Iss. 10/2005) are also provided for ease of your review.

a. GENERAL

i. As requested, the term "the" associated with the drug name "fentanyl transdermal system" has been deleted throughout the text.

ii. A hyphen has been added after the prefix "post" or "pre" throughout the text.

b. DESCRIPTION

We have included the requested text "Before use, a protective liner covering the adhesive layer is removed and discarded." immediately prior to the schematic diagram of the transdermal system.

c. CLINICAL PHARMACOLOGY - Pharmacokinetics

i. Figure – Revised the title to include "A".

ii. Table A - Revised the title to include "A".

d. PRECAUTIONS – Pregnancy: Pregnancy category C:

The subsection heading has been revised to read "Pregnancy: Teratogenic Effects: Pregnancy Category C".

e. DOSAGE AND ADMINISTRATION

i. Special Precautions – Underlined the second paragraph.

ii. Dose Titration – Revised the third paragraph in accord with the requested text.

f. PATIENT INFORMATION LEAFLET

a. What is fentanyl transdermal system? – 1st paragraph:

Added "opioid", as instructed.

b. How and where to apply fentanyl transdermal system – 1st bullet after the instruction #3:

As requested, instructions on how to open the blister have been included.

Please note that for completeness, we have included the final print version (Iss. 9/2006) of the (b) (4) in both Word and PDF formats. One (b) (4) will be provided in each carton.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
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May 3, 2007

ORIG AMENDMENT

N | AA

UNSOLICITED CMC AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED

MAY 4 2007

OGD

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
UNSOLICITED CMC AMENDMENT –
NOTIFICATION OF UPDATES TO THE DRUG SUBSTANCE DMF

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced, pending Abbreviated New Drug Application. We have been informed by the drug substance manufacturer, (b) (4) (b) (4), that they have updated their DMF # (b) (4). Please refer to **Attachment 1** which contains a letter from the drug substance manufacturer indicating that the update to the DMF for Fentanyl (b) (4) was submitted to the FDA on December 12, 2006.

In conjunction with the drug substance manufacturer's DMF updates, our documentation has been updated as follows:

- Please note that although the following material names may be used interchangeably, we have revised our reference to the material name from "(b) (4)" to (b) (4) as this is representative of the terminology used by the drug substance manufacturer. The revised drug substance specification sheet is provided as **Attachment 2**.

- The specifications for the (b) (4) Impurities ((b) (4) (b) (4)) have been listed separately and the drug substance manufacturer has generated and validated an HPLC method for the testing of these impurities. Please note that these impurities were previously listed and tested under the test for Impurities (b) (4). Additionally, the specifications for the (b) (4) Impurities (HPLC) have been (b) (4) as follows:

(b) (4) Impurity	Previous Specification	Current Specification (b) (4)

Please refer to **Attachment 2** for the updated drug substance specification sheet. For comparative purposes, the drug substance manufacturer's specifications are provided as **Attachment 3**. Please find enclosed, as **Attachment 4**, the drug substance manufacturer's validated HPLC method for the (b) (4) Impurities as well as an AVEVA method validation report which provides an abbreviated validation of the method to reflect the difference in (b) (4) and equipment. We hereby commit that all future testing of the drug substance will incorporate the method and specifications provided herein.

- The referenced retest period for the drug substance was revised from (b) (4) from date of manufacture" to (b) (4) from date of manufacture". Please note this change was made in accord with information provided by the drug substance manufacturer. The documentation detailing the (b) (4) of the expiration date for Fentanyl (b) (4) is provided in **Attachment 5**.

This information is submitted toward the continued review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson /pe

PE/jmd
Enclosures

TEVA

ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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July 27, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/A

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
TELEPHONE AMENDMENT – RESPONSE TO JULY 13, 2007 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a July 13, 2007 telephone contact with Shahnaz Read of the Office of Generic Drugs. Specifically, we were requested to add the following parameters to the routine test requirements for the polyisobutene adhesives: (b) (4)

Additionally, we were requested to re-evaluate our method and specification for (b) (4) testing.

With regard to the request for additional testing of the polyisobutene adhesives, we provide the following:

Please note that (b) (4) (the supplier of the (b) (4) adhesives) does not perform these tests on a routine basis and considers the associated methodology proprietary. As there are no current plans to source these adhesives from another supplier, we believe the following proposal addresses the immediate concerns of the Agency while providing a commitment to establish the requested methods and specifications.

We hereby commit that we will only source the polyisobutene adhesives (b) (4) (b) (4) from (b) (4) until such time that methods and specifications have been established for the requested parameters. Additionally, (b) (4) has provided documentation (**Attachment 1**) which indicates that there is no intent to carry out substantial changes in the production process of (b) (4), thereby ensuring consistent manufacture and quality of the adhesives. Additionally, (b) (4) is committed to providing notification of any manufacturing changes which may affect the quality of the adhesives. In conjunction with the above, we commit to develop and validate methods for the requested parameters as well as to generate appropriate specifications. This information will be submitted for FDA review and comment as soon as it becomes available. We propose that the information be provided via a prior approval supplement, following approval of the application, and prior to adding any new supplier of the polyisobutene adhesives.

With regard to the request to re-evaluate our method and specification for (b) (4) testing, we provide the following:

Based on the type of testing, changes to the methodology are limited to sample test (b) (4). In accord with the Agency's recommended specification of (b) (4), modifications were made to the method and the results are provided in **Attachment 2**. Please note that the method **(Attachment 3)** has been revised with regard to both sample test (b) (4). For ease of review, a summary of the changes is provided below.

Strength	Previous (b) (4) Test Parameters	Current (b) (4) Test Parameters
25 µg/hr	(b) (4)	
50 µg/hr		
75 µg/hr		
100 µg/hr		

Please note that due to the finished product patch (b) (4) of the lowest strength (25 µg/hr) a sample (b) (4) cannot be incorporated.

In conjunction with the revisions to the (b) (4) test parameters, the specification for (b) (4) has been revised as follows. The revised specification sheets are provided in **Attachment 4**.

Test	Previously Proposed Specification	Currently Proposed Specification
(b) (4)		

In accord with ASTM guidance, the reported value will be the average of triplicate testing.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned telephone contact. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson PZ

PE/jmd
Enclosures

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Debra Catterson PROJECT MANAGER: (240) 276-8963
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Clinical Review Team, regarding your ANDA 77-449 for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr.

The information request is presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 77-449

To: **TEVA Pharmaceuticals USA**

Drug: **Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr**

From: **Sarah Ho, PharmD**
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: **August 10, 2007**

Re: **Request for Information**

In order to facilitate the review of your skin irritation, sensitization and adhesion study for ANDA 77-449 for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr, please provide the following information:

A. The following comment pertains to study 770-0407-01:

   Your protocol provides for "an individual application site to be discontinued from further application if irritation of ≥ 3 was present in the dermal response score, or if an F, G, or H in the surface score was obtained." Please provide information concerning discontinuation of an application site due to excessive irritation: a list of subject and test article/treatment code for which an application site was discontinued, date and application number when the site was discontinued, and if subsequent patches were applied to a new site.

B. The following comments pertain to study 770-0407-03:

   1. Please provide copies of the CRFs and the specific reasons why the following subjects were discontinued from the study: Subjects 65, 69, 75, 90, 95, 114, 116, 169, 177, 178, 195, 213, 217, and 218.

   2. The following subjects were reported to have an adhesion score of 4 (0% adhered - test system detached). Please provide additional information regarding the patches that were detached (i.e., the length of time that the patches were detached, application number of the detached patch) for these subjects:

a. Test Article A: Subjects 1, 8, 11, 14, 43, 44, 51, 59, 60, 72, 78, 88, 89, 91, 94, 95, 104, 106, 107, 114, 116, 121, 122, 130, 132, 134, 139, 143, 145, 148, 152, 154, 155, 158, 163, 164, 172, 174, 179, 200, 201, 209, 210, and 213.

b. Test Article B: Subjects 9, 11, 21, 24, 28, 31, 38, 46, 49, 52, 54, 59, 72, 74, 88, 89, 91, 94, 95, 101, 102, 106, 114, 116, 119, 122, 124, 126, 127, 132, 143, 145, 148, 152, 154, 158, 160, 162, 163, 175, 186, 189, 192, 200, 201, 205, 208, 210, 213, 216, and 220.

3. Please provide the time point at which the challenge patch became detached for the following subjects: Subject 8, 10, 14, 19, 28, 30, 44, 89, 94, 106, 124, 126, 127, 148, 154, 158, 200, 208, and 220.

4. Your protocol provides for a "Re-Challenge Period." Please provide the results for all subjects that participated in this "Re-Challenge Period".

5. Please provide the follow-up data for Subject 116 and the outcome of her pregnancy.

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

/s/

Dena Hixon

8/10/2007 03:53:29 PM

ORIG AMENDMENT
N\AB

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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August 30, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCY AMENDMENT

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
BIOEQUIVALENCY AMENDMENT - RESPONSE TO AUGUST 10, 2007 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated August 10, 2007. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). Please note that your comments have been addressed in the order in which they were presented in the aforementioned correspondence.

Please note that your comments have been addressed by PRACS Institute, Ltd., the contract research organization which conducted the referenced studies (770-0407-01 & 770-0407-03).

A. Regarding study 770-0407-01:

The response, supplied by PRACS Institute, Ltd., is provided as **Attachment 2**.

B. Regarding study 770-0407-03:

1. Copies of the requested CRFs are provided on a disc contained in **Attachment 2**. The response (**Attachment 3**) from PRACS Institute, Ltd. contains the specific reasons for why subjects were discontinued.

2. Regarding patches that were detached:

   a. Please refer to the response (**Attachment 3**) from PRACS Institute, Ltd. regarding patches that were detached for Test Article A.

   b. Please refer to the response (**Attachment 3**) from PRACS Institute, Ltd. regarding patches that were detached for Test Article B.

3. Please refer to the response (**Attachment 3**) from PRACS Institute, Ltd. regarding the time point at which the challenge patch became detached.

4. Please refer to the response (**Attachment 3**) from PRACS Institute, Ltd. regarding the "Re-Challenge Period".

5. Please refer to the response (**Attachment 3**) from PRACS Institute, Ltd. regarding the follow-up data for Subject 116 and the outcome of her pregnancy.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Teva Pharmaceuticals TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 21, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25 mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **two** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-449 APPLICANT: Teva pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal system,
25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. We agree with your proposed dissolution method and specification as follows:

   The in vitro dissolution testing should be conducted in 500 ml (for the 25 and 50 µg/hr strengths) and 900 ml (for the 75 and 100 µg/hr strengths)of Phosphate buffer pH 6.8 at 32°C±0.5°, using USP apparatus 6 (cylinder) at 50 rpm. The test product should meet the following specification:

   2 hours: (b) (4)
   6 hours:
   12 hours:
   72 hours:

   (Please note that the specifications are presented as percentage of **labeled amounts** per patch)

   Your proposed acceptance criteria are acceptable (see below). However, you should include the limit for the average values at 2, 6 and 12 hrs and it should also be corrected that at L3 level, not more than 2 of the 24 units are outside the L2 range and none of the units is outside the L3 range for the 2. 6 and 12 hour time point.

Proposed Acceptance Criteria

Level	L_1			L_2			L_3		
Type	Range			Range			Range		
	Acceptance Criteria			Acceptance Criteria			Acceptance Criteria		
Time Point	Low Range		High Range	Low Range		High Range	Low Range		High Range
2 hr	(b) (4)		(b) (4)	(b) (4)		(b) (4)	(b) (4)		(b) (4)
6 hr									
12 hr									

Level	L_1	L_2	L_3
Type	Limit	Limit	Limit
	Acceptance Criteria	Acceptance Criteria	Acceptance Criteria
Time Point		Average of 12 units is NLT (b) (4)	Average of 24 units is NLT (b) (4)
72 hr	No individual value is LT (b) (4)	No individual value is LT	NMT 2 units of the 24 is LT None of the units is LT

2. Your submitted toxicology information pertaining to the adhesives is currently under review. Therefore, the test formulation is still not acceptable pending the FDA Pharmacology/Toxicology review.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
11/19/2007 04:13:43 PM
Signing for Dale P Conner

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

November 28, 2007

RECEIVED
NOV 29 2007
OGD

BIOEQUIVALENCY AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N AB

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
BIOEQUIVALENCY AMENDMENT - RESPONSE TO NOVEMBER 19, 2007 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated November 19, 2007. For ease of your review, please find attached a copy of the November review letter. We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Deficiencies

1. We acknowledge that the Division of Bioequivalence accepts our proposed dissolution method and specifications. We also note that our proposed acceptance criteria were found acceptable. However, in accord with your request the criteria have been updated to include the requested revisions.

Acceptance Criteria

Level	**L_1**			**L_2**			**L_3**		
Type	**Range**			**Range**			**Range**		
	Acceptance Criteria			Acceptance Criteria			Acceptance Criteria		
Time Point	**Low Range**		**High Range**	**Low Range**		**High Range**	**Low Range**		**High Range**
2 hr	(b) (4)		(b) (4)	(b) (4)		(b) (4)	(b) (4)		(b) (4)
6 hr									
12 hr									
	No individual unit lies outside the L1 range.			The average value of 12 units is not outside the L1 range. No individual unit lies outside the L2 range.			The average value of 24 units is not outside the L1 range. Not more than 2 of 24 units are outside the L2 range. No individual unit lies outside the L3 range.		

Level	**L_1**	**L_2**	**L_3**
Type	**Limit**	**Limit**	**Limit**
	Acceptance Criteria	Acceptance Criteria	Acceptance Criteria
Time Point		Average of 12 units is NLT (b) (4)	Average of 24 units is NLT (b) (4) NMT 2 units of the 24 is LT
72 hr	No individual value is LT (b) (4)	No individual value is LT	None of the units is LT

2. We acknowledge that the submitted toxicology information is currently under review and that a satisfactory assessment of said information is required for acceptance of the formulation.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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philip.erickson@tevausa.com

March 14, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

LABELING AMENDMENT

N-000-AF

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
LABELING AMENDMENT – REVISED FINAL PRINT LABELING

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced, pending Abbreviated New Drug Application to provide revised final print labeling for the blister, carton, insert, and patient information leaflet as well as the addition of a medication guide. The proposed changes were made in accord with the most current labeling for Duragesic®, approved on February 7, 2008.

Please find enclosed, a disk containing the following revised final print labeling.

Blisters
The disk contains electronic versions of the final print blister labeling (Iss. 2/2008) in both PDF and Word formats. Please note that due to the extensive changes in the current RLD pouchstock labeling, a PDF of the side-by-side comparison of Teva's blister labeling to the current RLD pouchstock labeling is provided. For completeness, a PDF of the RLD pouchstock labeling is also provided.

Cartons
The disk contains electronic versions of the final print carton labeling (Iss. 2/2008) in both PDF and Word formats. Please note that due to the extensive changes in the current RLD carton labeling, a PDF of the side-by-side comparison of Teva's carton labeling to the current RLD carton labeling is provided. For completeness, a PDF of the RLD carton labeling is also provided.

Insert
The disk contains electronic versions of the final print insert (Iss. 2/2008) in both PDF and Word formats, as well as a comparison to our last submitted insert (Iss. 3/2007) in PDF format. Please note that the final print insert also contains the information for use and medication guide.

Information for Use

The disk contains an electronic version of the final print information for use labeling (Iss. 2/2008) in Word format. Please note that the PDF final print insert contains the information for use labeling in PDF format. Due to the extensive changes in the current RLD labeling, a PDF of the side-by-side comparison of Teva's information for use labeling to the current RLD information for use labeling is provided. For completeness, a PDF of the RLD information for use labeling is also provided.

Medication Guide

The disk contains an electronic version of the final print medication guide (Iss. 2/2008) in Word format. Please note that the PDF final print insert contains the medication guide in PDF format. Please note that as this is an addition to the previously existing labeling, a PDF of the side-by-side comparison of Teva's medication guide to the current RLD medication guide is provided. For completeness, a PDF of the RLD medication guide is also provided.

Please note that there are no proposed labeling changes or revisions to the unit backing or the (b) (4) accompanying each carton. These labeling components were last submitted via our April 26, 2007 labeling amendment to this application.

This information is provided for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/PE

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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philip.erickson@tevausa.com

June 3, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCE AMENDMENT

N-000-AB

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr, 50 µg/hr, 75 µg/hr and 100 µg/hr
BIOEQUIVALENCE AMENDMENT – RESULTS OF AN OVERLAY STUDY

Dear Mr. Buehler:

We submit herewith a bioequivalence amendment to the above-referenced, pending Abbreviated New Drug Application. This submission contains the results of an overlay study which demonstrates that our Fentanyl Transdermal System results in equivalent bioavailability of the drug product with or without a Bioclusive® overlay. The study provided herein (**Attachment 1**) is presented in accord with the current labeling for the reference-listed drug, Duragesic®, approved on February 7, 2008. The RLD labeling now includes information relating to the use of a transparent adhesive film dressing in the event that the adhesion of the patch poses an issue. Teva conducted the enclosed study due to our belief that the Agency will require all generic applicants to incorporate the possible use of an overlay in the product's labeling and demonstrate that said use of an overlay does not impact the product's overall bioequivalence.

The following information is provided in support of this amendment:

Attachment 1:

- ♦ Financial Disclosures
- ♦ Disk containing the following:
  - a) Bioavailability Report
  - b) Bioanalytical Report
  - c) Bioequivalence Summary Tables

The clinical and analytical facilities used to perform the study are identified below:

Clinical Facility:
NOVUM Pharmaceutical Research Services
3320 Walnut Bend Lane
Houston, TX 77042-4712

Analytical Facility:
(b) (4)

Attachment 2: Certificate of Analysis for Batch # 36623, the lot used in the Overlay study.

Please note that our revised labeling which incorporates the information pertaining to the use of an overlay will be submitted under separate cover.

This information is submitted toward the review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/PE

PE/jmd
Enclosures

18.1

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
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philip.erickson@tevausa.com

June 18, 2008

ORIG AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ADDENDUM TO
MARCH 14, 2008
LABELING AMENDMENT

RECEIVED

JUN 19 2008

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
ADDENDUM TO MARCH 14, 2008 LABELING AMENDMENT

Dear Mr. Buehler:

We submit herewith an addendum to our March 14, 2008 labeling amendment to the above-referenced, pending Abbreviated New Drug Application to provide revised final print labeling for the insert, medication guide and patient information leaflet. Teva's previously submitted final print labeling has been revised in order to include information pertaining to the potential use of a transparent adhesive film dressing in the event that the adhesion of the patch poses an issue. This revision is in accord with our June 3, 2008 bioequivalence amendment that provided an overlay study which demonstrates that our Fentanyl Transdermal System results in equivalent bioavailability of the drug product with or without a Bioclusive® overlay.

The intent of this submission and the labeling provided herein is to replace the final print insert, information for use, and medication guide (Iss. 2/2008) submitted in the March 14, 2008 labeling amendment.

Please find enclosed a disk containing the following revised final print labeling.

Insert
The disk contains Teva's final print insert (Iss. 5/2008) in both PDF and Word formats. Due to the extensive changes in the current RLD labeling since our last submission, a PDF of the side-by-side comparison of Teva's insert to the current RLD insert is provided. Please note that the PDF of the final print insert also contains the information for use and medication guide.

Information for Use
The disk contains the final print information for use labeling (Iss. 5/2008) in Word format. Due to the extensive changes in the current RLD labeling, a PDF of the side-by-side comparison of Teva's information for use labeling to the current RLD information for use labeling is provided. Please note that the PDF of the final print insert contains the information for use labeling in PDF format.

Medication Guide

The disk contains an electronic version of the final print medication guide (Iss. 5/2008) in Word format. Please note that the PDF of the final print insert contains the medication guide in PDF format. Please note that as this is an addition to the previously existing labeling, a PDF of the side-by-side comparison of Teva's medication guide to the current RLD medication guide is provided.

Please note that there are no proposed revisions to the unit backing or the (b) (4) accompanying each carton. These labeling components were last submitted via our April 26, 2007 labeling amendment to this application. Additionally, we do not propose any changes to the final print blister or carton labeling provided in our March 14, 2008 labeling amendment.

This information is provided for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

Telephone Fax

ANDA77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8974

TO: Teva Pharmaceuticals USA TEL: 215-591-3000

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transderaml system.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

Labeling Comments:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-449 Date of Submission: April 26, 2007, March 14, 2008 and June 18, 2008

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

Labeling Deficiencies:

1. GENERAL COMMENT

   Please be advised that the innovator's proposal for the Risk Management Plan (RMP) submitted as a labeling supplement is still under review by the Agency. You may be required to submit the similar proposal upon approval of the innovator's RMP.

2. BLISTER - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   a. As addressed in the last deficiency letter, the text on your proposed blister appears too cluttered, particularly with inclusion of new safety information approved for Durasegic® Patch. This may lead to potential medication error. In addition, the direction for removing fentanyl transdermal system from the blister is not very clear as appearing in the "Instructions for Applying Fentanyl Transdermal System". This may predispose the system to cutting or damaging when removing from the blister as the patient needs to cut through blister taking care not to cut through the fentanyl transdermal system according to your proposal.

   b. For the reasons described above, we strongly recommend that you reconfigure your packaging to be the same as the innovator's *i.e.* pouch, rather than blister and/or comment. If you change the packaging as directed, then you need to submit the CMC information associated with the new packaging. In addition, please revise all labeling pieces accordingly.

   c. "USUAL DOSAGE" rather than "DOSAGE"

3. CARTON - 5 systems

   a. See comment 2(c) above.

   b. Please relocate the text and lines associated with recording of narcotic use to the back panel to be the same as the innovator's. We believe that the text on the side panel may be subject to overlook.

4. UNIT BACKING

   The text on the blister backing for the 50 mcg/hr and 75 mcg/hr submitted April 26, 2007 is not sufficiently prominent. Please enhance the prominence that the name and strength of the drug product is readily legible.

5. INSERT

   a. GENERAL

      i. Please replace either "Duragesic®" or "Durasegic® Patch" found in the innovator's labeling with "fentanyl transdermal system". Please be advised that the established name of your drug product is "fentanyl transdermal system", not "(b) (4)".

ii. We note that your drug product has matrix system as opposed to the innovator's reservoir system, yet you included the same text found in the innovator's labeling "Using a patch that is cut, damages, or changed in any way can expose the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal." in many places throughout the insert labeling. Is this an accurate statement for your drug product? This information may be specific to the reservoir system. Please delete and/or comment.

b. CLINCIAL PHARMACOLOGY - Pharmacokinetics:

We note that you included information regarding the pharmacokinetic study with or without overlay (*i.e.,* Bioclusive™ Overlay) to be in accordance with the innovator's labeling. We acknowledge that you submitted the overlay study to the Agency on June 3, 2008, which is under review. Please be advised that we defer the approval of your proposal pending your pharmacokinetic study associated with overlay.

c. PRECAUTIONS - Information for Patients, item #8:

See comment 5(b) above.

d. DOSAGE AND ADMINISTRATION

i. Special Precautions:

See comment 5(b) above.

ii. 7th paragraph, last sentence:

…Drug Interaction; WARNINGS and PRECAUTIONS… [add "WARNINGS"]

iii. Dose Selection - Table D:

Please include the proprietary names as appearing in the innovator's labeling and include the disclaimer statement for these names.

6. MEDICATION GUIDE

a. GENERAL

See comment 5(a) above.

b. TITLE

It is preferable to include the term "Rx Only".

c. How should I use…Transdermal System - 2nd bullet:

See comment 5(b) above.

d. Please include the name and place of business at the end of the medication guide.

7. INSTRUCTIONS FOR APPLYING A FENTANYL TRANSDERAMAL SYSTEM

a. See comment 5(a) above.

b. Applying a Fentanyl Transdermal system - Item #3:

See comment (2) under BLISTER above. The instruction for removal of the

system from the blister without causing any potential damage is not very clear to follow.

c. Applying a Fentanyl Transdermal System -Item #5, 3rd bullet:

See comment 5(b) above.

Revise your labeling, as instructed above, and submit electronically in final printed format. We will not ask final printed labeling pending the issue associated with the overlay study.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
7/2/2008 07:27:45 PM
Lillie Golson for Wm. Peter Rickman

MINOR AMENDMENT

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Laura Longstaff FDA CONTACT PHONE: (240) 276-8566

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 21, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr.

Reference is also made to your amendment dated January 3, April 3, April 16, April 24, May 3, and July 27, 2007.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**1**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-449 APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT:

The deficiencies presented below represent MINOR deficiencies.

1. We acknowledge your commitment to develop and validate methods for the testing of [redacted] (b) (4) to generate the appropriate specifications and submit the information as soon as it becomes available. Please submit the methods, test results and specifications for [redacted] (b) (4) prior to approval.

2. Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. You are referred to the letter posted on the Office of Generic Drugs website. The following data package should be submitted:

   For each excipient in the formulation:
   - manufacturer's COA including solvents
   - applicant's updated COA for the excipient including solvent specification (solvent identity, acceptance criteria and analytical method). Loss on drying would be acceptable if only Class 3 solvent/s is used in the manufacture of an ingredient
   - applicant's test data for solvents, including data for class 3 solvents, should be submitted for the excipients
   - method validation data if non-USP methods are used
   - applicant must demonstrate that the excipient meets ICH Q3C option 1 or option 2

   The finished product specification should be updated to state compliance with USP<467>.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Glen Smith

7/9/2008 09:37:50 AM

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

August 26, 2008

ORIG AMENDMENT

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

77-000-AF

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr
LABELING AMENDMENT - RESPONSE TO JULY 2, 2008 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced, pending Abbreviated New Drug Application in response to a July 2, 2008 review letter. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

RECEIVED
AUG 27 2008
OGD

Labeling Deficiencies:

1. GENERAL COMMENT

   We note that the innovator's proposal for a Risk Management Plan (RMP) is currently under review by the Agency and acknowledge that we may be required to submit a similar proposal upon approval of the innovator's RMP.

2. BLISTER – 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

   Please find enclosed, as **Attachment 2**, a disk containing final print blister labeling (Iss. 7/2008) in both PDF and Word for each strength, along with a comparison to that of our last submitted blister labeling (Iss. 2/2008).

   a. Please note that it is our position that the blister labeling for the 75 mcg/hr and 100 mcg/hr strengths is no more cluttered in appearance than the brand's pouch labeling. The size of the printable area for the blister labeling of the 50 mcg/hr has been increased by printing onto the heat seal area. This change did not require any modification to the blister package itself. In order to expand the printable area for

the 25 mcg/hr strength, we have reconfigured the blister package to incorporate an expanded flange that is of comparable size to the 50 mcg/hr strength. There has been no change in the size/shape of the blister cavity, only an extension of the blister flange to generate additional printable area. The updated blister drawing is provided in **Attachment 3**. This change, in addition to the fact that similar information is duplicated on the other accompanying pieces of labeling (carton and insert), minimizes the potential for medication error.

With regard to the directions for removing the fentanyl transdermal system from the blister, we believe that the instructions are clear and easy to follow. The patch does not fill the entire blister cavity and therefore allows the patient to visibly see the patch and thereby avoid cutting or damaging it. For demonstration purposes, we've provided five generic blister samples (**Attachment 4**) representing each strength and encourage the reviewer to open the blisters according to the current instructions. This exercise provides evidence that the patient is able to open the blister without cutting or damaging the patch itself. Please note that the sample blister package for the 25 mcg/hr strength is representative of the originally proposed design and does not include the expanded printable area discussed above.

b. With regard to your recommendation to reconfigure the packaging into a pouch, rather than a blister, it is our assertion that our blister packaging provides benefits which are not available or realized through the use of a pouch. The benefits are outlined below.

   i. The RLD labeling instructs patients to open a pouch by tearing the "pouch along the dotted line, starting at the slit". The labeling for Mylan's approved generic product instructs the patient to "tear open the pouch". Based upon this, the pouch configuration offers very little, if any, child resistant properties. The blister packaging proposed within Teva's application requires an individual to actually cut the blister in order to gain access to the patch. It is our belief that for a product which has safety concerns regarding accidental exposure or keeping the product out of the hands of children, a blister package provides far greater protective properties than a tear-open pouch.

   ii. The fact that Teva's blister packaging allows the patient to verify the strength of the patch prior to removing it from the blister is an additional advantage that the pouch configuration does not afford the patient. The labeling instructs the patient to verify that they have received the proper "dose patch or patches that were prescribed". In addition to the carton labeling and blister labeling, the patient can verify the strength visually through the blister without opening the protective blister packaging. The only way to verify the contents of the pouch is to physically tear it open.

iii. The blister cavity is designed to accommodate the size of the patch. Therefore, each strength of the patch is designed to correspond only with its respective blister. This provides assurance that the proper strength of each patch is contained within its respective blister. The same cannot be said for the pouch, as there would be no way to visually verify that a pouch labeled as 100 mcg/hr did indeed contain a patch of said strength.

iv. The design of the blister cavity also adds a layer of protection that helps prevent the patch from being compressed during storage such that cold flow (drug matrix) or leakage (reservoir) does not occur. A pouch offers no such protective properties.

Based on the above, we respectfully decline your recommendation to reconfigure our packaging into pouches. Additionally, it should be noted that there is no regulatory requirement for a generic product to have the same packaging as the RLD.

c. As instructed, "DOSAGE" was revised to "USUAL DOSAGE".

3. CARTON – 5 systems

Please find enclosed, as **Attachment 2**, a disk containing final print carton labeling (Iss. 7/2008) in both PDF and Word for each strength, along with a comparison to that of our last submitted carton labeling (Iss. 2/2008).

a. As instructed, "DOSAGE" was revised to "USUAL DOSAGE".

b. The text and lines associated with the recording of narcotic use have been relocated to the back panel.

4. UNIT BACKING

Samples of the unit backing and the inks incorporated therein have been submitted on two occasions, a June 5, 2006 labeling amendment and an April 26, 2007 labeling amendment. Further it is our understanding that the color of the inks used to identify the name and strengths is in accord with the color scheme employed by the RLD in their identification of the product and strengths. Therefore, we believe that the name and strength of the drug product are sufficiently prominent and readily legible. Due to market shortage we are unable to obtain brand patches to demonstrate this further. It should also be noted that the unit backing is the third piece of labeling which identifies the product name and strength. The carton, blister, and unit backing serve this purpose prior to wearing the patch itself.

5. INSERT

In accord with the changes noted below, please find enclosed, as **Attachment 2**, a disk containing the final print package insert (Iss. 7/2008) in both Word and PDF formats. Additionally, a PDF file comparing the revised package insert to the last submitted (Iss. 5/2008) is also provided for ease of your review. Please note that the PDF of the final print insert also contains the medication guide and patient instructions.

a. GENERAL

i. As requested, "Duragesic®" and "Duragesic® Patch" have been replaced with "fentanyl transdermal system".

ii. As suggested, information specific to the reservoir system has been deleted.

b. CLINICAL PHARMACOLOGY - Pharmacokinetics

We acknowledge that our overlay study is under review and approval is deferred pending the completion of the review.

c. PRECAUTIONS – Information for Patients, item #8

We acknowledge that our overlay study is under review and approval is deferred pending the completion of the review.

d. DOSAGE AND ADMINISTRATION

i. Special Precautions:

We acknowledge that our overlay study is under review and approval is deferred pending the completion of the review.

ii. 7th paragraph, last sentence:

As recommended, we have added "WARNINGS" to ...Drug Interaction; WARNINGS and PRECAUTIONS...

iii. Dose Selection – Table D

As requested, the proprietary names have been included along with the disclaimer statement for these names.

6. MEDICATION GUIDE

In accord with the changes noted below, please find enclosed, as **Attachment 2**, a disk containing the final print medication guide (Iss. 7/2008) in both Word and PDF formats. Additionally, a PDF file comparing the revised medication guide to the last submitted (Iss. 5/2008) is also provided for ease of your review. Please note that the PDF of the final print insert also contains the medication guide and patient instructions.

a. GENERAL

As requested, "Duragesic®" and "Duragesic® Patch" have been replaced with "fentanyl transdermal system". As suggested, information specific to the reservoir system has been deleted.

b. TITLE

The term "Rx only" is included.

c. How should I use…Transdermal System – 2nd bullet:

We acknowledge that our overlay study is under review and approval is deferred pending the completion of the review.

d. The name and place of business is incorporated at the end of the medication guide.

7. INSTRUCTIONS FOR APPLYING A FENTANYL TRANSDERMAL SYSTEM

In accord with the changes noted below, please find enclosed, as **Attachment 2**, a disk containing the final print patient instructions (Iss. 7/2008) in both Word and PDF formats. Additionally, a PDF file comparing the revised patient instructions to the last submitted (Iss. 5/2008) is also provided for ease of your review. Please note that the PDF of the final print insert also contains the medication guide and patient instructions.

a. As requested, "Duragesic®" and "Duragesic® Patch" have been replaced with "fentanyl transdermal system". As suggested, information specific to the reservoir system has been deleted.

b. Please refer to our response to comment 2(a) regarding the instructions for removal of the system from the blister.

c. Applying a Fentanyl Transdermal System – Item #5, 3rd bullet:

We acknowledge that our overlay study is under review and approval is deferred pending the completion of the review.

Please note that there are no proposed revisions to the (b) (4) accompanying each carton. This labeling component was last submitted in final print format via our April 26, 2007 labeling amendment to this application.

In light of the continued market shortage, we believe it to be appropriate and necessary that Teva's applications for a quality drug product be afforded expedited review.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Eriksen/PE

PE/jmd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

September 18, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

ORIG AMENDMENT
N. AM

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
MINOR AMENDMENT - RESPONSE TO JULY 9, 2008 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a July 9, 2008 review letter. For ease of review, please find enclosed a copy of this letter (**Attachment 1**). We have addressed your comments in the order in which they were presented in the aforementioned correspondence.

Deficiencies

1. In conjunction with the aforementioned review letter and the commitment contained in our July 27, 2007 telephone amendment, we've developed and validated methods for the requested testing of the [redacted] (b) (4) The methods and their corresponding validation are outlined below:

[redacted] (b) (4) **(Attachment 2)**

- Standard Testing Procedure [redacted] (b) (4)
- Method Validation Report (Document No [redacted] (b) (4))

[redacted] (b) (4) **(Attachment 3)**

- Method: [redacted] (b) (4)
- Method Validation Report (Protocol No. [redacted] (b) (4)

[redacted] (b) (4) **(Attachment 4)**

- Standard Testing Procedure [redacted] (b) (4)
- Method Validation Report (Document No. [redacted] (b) (4)

RECEIVED
SEP 19 2008
OGD

Following this page, 3 pages withheld in full - (b)(4)

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Crickmore

PE/jmd
Enclosures

BIOEQUIVALENCY COMMENTS

ANDA 77-449

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Debra Catterson PROJECT MANAGER: (240) 276-8963
(240) 276-8966 (fax)

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 17, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr.

Reference is also made to your amendments dated March 21, 2005; April 20, 2005; June 15, 2005; January 31, 2007; and August 30, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has provided comments which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-449 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 77-449 are adequate to demonstrate that the irritation potential of Teva Pharmaceuticals USA's (Teva) placebo Fentanyl Transdermal System (TDS), 25 mcg/hr is no worse than that of positive controls (0.02% and 0.04% sodium lauryl sulfate) of low irritancy.

The data also demonstrate minimal potential of Teva's placebo Fentanyl TDS to induce sensitization, as expected with use of the RLD, Duragesic®.

The data also demonstrate that the adhesive performance of Teva's Fentanyl TDS is at least as good as that of the RLD.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit

9/26/2008 03:37:02 PM

M E M O R A N D U M

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

FROM: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence 2
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Approvability of ANDA 77-449 for Fentanyl Transdermal Systems (TDS)

TO: ANDA 77-449 for Fentanyl Transdermal System by TEVA

BACKGROUND:

Mylan Technologies Inc. ("Mylan") submitted a citizen petition dated March 16, 2006, Docket # 2006P-0440. The petition argues that fentanyl transdermal systems may have problems "sticking" to the skin and that the use of an unapproved and untested overlay to help the patch stick to the skin may cause adverse consequences. Therefore, Mylan requests that the FDA require all applicants and holders of approved applications for fentanyl transdermal systems to conduct a study to support the safe and appropriate use of an overlay with their respective patch, as Mylan was undertaking at the time the petition was submitted.

Duragesic fentanyl transdermal system, the reference listed drug (RLD), was approved as safe and effective under NDA 19-813 on August 7, 1990. The innovator firm submitted a pharmacokinetic study on October 4, 2006 demonstrating that fentanyl absorption from the Duragesic patch with an overlay is equivalent to fentanyl absorption from the Duragesic patch when applied without an overlay.

Mylan markets an approved generic fentanyl transdermal system under ANDA 76-258 that references Duragesic. Mylan submitted a pharmacokinetic study on November 10, 2006 demonstrating that fentanyl absorption from its generic fentanyl patch with an overlay is equivalent to fentanyl absorption from the patch when applied without an overlay.

Teva also submitted a pharmacokinetic study to ANDA 77-449 on June 3, 2008 demonstrating that fentanyl

absorption from its generic fentanyl patch with an overlay is equivalent to fentanyl absorption from the patch when applied without an overlay.

QUESTION PRESENTED:
Does the pendency of the Mylan petition preclude approval of the pending ANDA for Teva's fentanyl transdermal system?

BRIEF ANSWER:
The pendency of the Mylan petition does not preclude approval of Teva's ANDA 77-449 for fentanyl transdermal systems.

DISCUSSION:
As noted above, both the reference listed drug for this ANDA, Duragesic, and Mylan's generic fentanyl transdermal system have been approved as safe and effective. The sponsors of both of these approved products have conducted pharmacokinetic studies demonstrating that the absorption of fentanyl from their products is equivalent with and without the use of an overlay. Teva, the sponsor of the pending ANDA 77-449 has also submitted a pharmacokinetic study showing that the absorption of fentanyl from its product is also equivalent with and without the use of an overlay. Therefore, Mylan's request that FDA require all applicants for fentanyl transdermal systems to conduct a study to support the safe and appropriate use of an overlay with their respective patch has already been fulfilled by the sponsor of the pending application.

CONCLUSION:
Because Teva has already conducted a study to support the safe and appropriate use of an overlay with their respective patch as requested by Mylan to support approval of any application for a transdermal fentanyl product, there is no reason to withhold approval of ANDA 77-449 based on the considerations raised by the petition.

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

/s/

Dena Hixon
10/7/2008 02:02:36 PM
MEDICAL OFFICER

Barbara Davit
10/7/2008 04:47:08 PM
BIOPHARMACEUTICS

Gary Buehler
10/8/2008 12:42:23 PM
DIRECTOR

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

October 28, 2008

N-000-MC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MISCELLANEOUS CORRESPONDENCE-
SPL FOR APPROVED ANDA 77-449

NAI
11/10/08

ANDA # 77-449
FENTANYL TRANSDERMAL SYSTEM, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h
MISCELLANEOUS CORRESPONDENCE – SPL FOR APPROVED ANDA 77-449

Dear Mr. Buehler:

We submit herewith miscellaneous correspondence to the above-referenced Abbreviated New Drug Application to provide our package insert, medication guide and patient instructions in SPL format. This labeling is provided in accord with a request contained within the October 20, 2008 approval letter for Fentantyl Transdermal System (ANDA # 77-449).

Enclosed herein please find a disk containing our approved final print package insert (Iss. 7/2008), medication guide (Iss. 7/2008) and patient instructions (Iss. 7/2008) in PDF and SPL formats. Please note that Iss. 7/2008 is the labeling that was approved for this file, and there have been no changes to the content of the labeling.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the request presented in the aforementioned approval letter. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jmd
Enclosures

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-449 Applicant Teva Pharmaceuticals USA
Drug Fentanyl Transdermal System, Strength(s) 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 9 OCT 2008 | Date 10/20/08
Initials MHS | Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# 19-813
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter:
Comments: ANDA submitted on 12/20/2004, BOS=Duragesic NDA 19-813, PIII to '580. RTR issued on 2/9/2005 for inactive ingredient issues. Firm responded to RTR on 6/16/2005- ANDA ack for filing on 6/16/2005 (LO dated 6/30/2005). 2nd Ack letter issued on 6/29/2005-this letter granted TEVA a filing date of 3/22/2005. There are no remaining patents or exclusivities which preclude approval of this ANDA. Application is eligible for Full Approval.

2. Project Manager, Laura Longstaff Team 9
Review Support Branch
Date 10/8/2008 | Date 10/15/08
Initials LAL | Initials sse

Original Rec'd date December 17, 2004
Date Acceptable for Filing December 20, 2004
Patent Certification (type)
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 10/8/2008
Date of Office Bio Review 9/22/08
Date of Labeling Approv. 10/14/2008
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer:
Date _____
Name/Initials _____

Labeling Team Leader:
Date 10/20/08
Name/Initials rlw/for

Final-printed labeling (FPL) fopund acceptable for approval 10/14/08.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 10/20/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this

drug product.

5. Div. Dir./Deputy Dir. Date10/17/08
Chemistry Div. I II OR III InitialsRCA
Comments:CMC O.K. 10% more drug than RLD, but judged O.K. by Bio - results O.K.

6. Frank Holcombe **First Generics Only** Date10/20/08
Assoc. Dir. For Chemistry Initialsrlw/for
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Duragesic-25, -50, -75 and -100
Ortho McNeil Janssen NDA 19-813 (004, 003, 002, 001)

8. Peter Rickman Date10/20/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: Bioequivalence study (fasting) on the 25 ug/hour strength)found acceptable 2/23/07. In-vitro dissolution testing for all 4 strengths also found acceptable. Waivers granted to the 50 mcg/hr, 75 mcg/hr and 100 mcg/hr strengths under 21 CFR 320.22(d)(2). Bio study testing sites have acceptable DSI inspection histories. Skin sensitization/irritation studies also reviewed and found acceptable 9/22/08. DSI inspection of study sites conducted at PRACS Dermatology LLC, San Diego, CA and PRACS Institute Ltd, Fargo, ND. Inspection completed without significant deficiencies. Report filed in DFS.

Bio study with and without overlay reviewed and found acceptable.

Statisdtical review completed and entered into DFS 4/2/08.

Pharmacology/Toxicology consult on amount of polyisobutene adhesive and (b) (4), and tolerance and toxicology studies for (b) (4) (b) (4) found acceptable (Pharm/Tox Consult #2) 8/1/07 - in DFS.

Final-printed labeling (FPL) found acceptable for approval 10/14/08.

CMC found acceptable for approval (Chemistry Review #4).

OR

8. Robert L. West Date 10/20/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ NoX☐; Pending Legal Action: Yes☐ No; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments: Acceptable EES dated 10/8/08 (Verified 10/20/08). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

There is currently a Citizen Petition submitted by Mylan for the agency to require that all applications for this drug product contain a study to support the safe use of the product with and without the use of an overlay. TEVA has conducted such a study. This study was reviewed and found acceptable. A memorandum to the record has been placed into the file (DFS) dated 10/8/08..

This ANDA is recommended for approval.

9. Gary Buehler Date 10/20/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Laura Longstaff Date10/20
Review Support Branch Initials se for

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
11:20Time notified of approval by phone
11:22amTime approval letter faxed

FDA Notification:
10/20/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
10/20/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 019813 Product 004 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2008
Patent and Generic Drug Product Data Last Updated: October 17, 2008

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

/s/

Simon Eng

10/20/2008 11:32:48 AM