

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-813/S044

Trade Name: Duragesic

Generic Name: Fentanyl

Sponsor: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Approval Date: 7/31/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S044

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019813/S-044

APPROVAL LETTER

Ortho-McNeil-Janssen Pharmaceuticals, Inc
(c/o) Johnson & Johnson Pharmaceutical Research and Development, LLC
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Attention: Harindra Abeyasinghe, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abeyasinghe:

Please refer to your January 30, 2009 supplemental new drug application, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Duragesic[®] (fentanyl transdermal system) 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

We acknowledge receipt of your submissions dated November 26, 2008, April 10 and 28, May 21, and July 15 and 20, 2009.

Your May 21, 2009 submission constituted a major amendment to your supplemental application.

This supplemental new drug application provides for a matrix formulation for the transdermal delivery of fentanyl.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical to the enclosed labeling text for the Package Insert, Information for Use, and Medication Guide. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 019813/S-044.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the sample enclosed carton and immediate container labels for all strengths, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 019813/S-044.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since Duragesic was approved on August 7, 1990 we have become aware, during the review of this supplement, of the possibility of (b) (4)

(b) (4) as compared to gel component of Duragesic. Such (b) (4) has a potential to increase the exposure to certain genotoxic impurities and result in a potential for altered risk of genotoxicity associated with exposure to the fentanyl drug substance impurity (b) (4)

We consider this information to be “new safety information” as defined in the Federal Food and Drug Administration Amendments Act (FDAAA).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of genotoxicity associated with exposure to the fentanyl drug substance impurity (b) (4) at the proposed levels.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1495-1. An in vivo mouse micronucleus assay for Impurity B.

The timetable you submitted via email on July 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	October 1, 2009
Study Completion Date:	January 1, 2010
Final Report Submission:	March 1, 2010

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF SECTION 506B OF THE FD&C ACT

We remind you of your postmarketing study commitments described in your email dated July 29, 2009. These commitments are listed below.

- 1495-2. To reduce the limit of quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of no more than (NMT) (b) (4) ppm.

Final report submission by January 31, 2010

- 1495-3. To reduce the limits of detection and quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated.

Final report submission by January 31, 2010

- 1495-4. To evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the levels of the material do not exceed 1.5 mcg/day (equivalent to (b) (4) ppm in the product).

Final report submission by January 31, 2010

- 1495-5. To evaluate the specificity of the assays used in the leachable/extractable studies.

Final report submission by January 31, 2010

- 1495-6. To conduct the Probe Tack test and submit the test method, validation report and specification.

Final report submission by December 31, 2009

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled “**Postmarketing Commitment Protocol**”, “**Postmarketing Commitment Final Report**”, or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

EXPIRATION DATING PERIOD

An expiry of 24 months is granted under the recommended storage conditions: Store at 25° (77°F); excursions permitted to 15 - 30°C (59 - 86°F).

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

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

Enclosures (4): Package Insert
Medication Guide
Information for Use
Carton and Container Labels

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

/s/

BOB A RAPPAPORT
07/31/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

LABELING

DURAGESIC® CII
(Fentanyl Transdermal System)

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

DURAGESIC® 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 (DURAGESIC®) may be a particular target for abuse and diversion.

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**

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.

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])

(See CONTRAINDICATIONS for further information.)

Since the peak fentanyl concentrations generally occur between 20 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 DURAGESIC® 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 DURAGESIC® 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 DURAGESIC® 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 (see PRECAUTIONS - Pediatric Use).

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. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose (see DOSAGE And ADMINISTRATION – Initial DURAGESIC® Dose Selection). Due to the mean half-life of approximately 20-27 hours, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is

concerned about increased risk of misuse, abuse, or diversion.

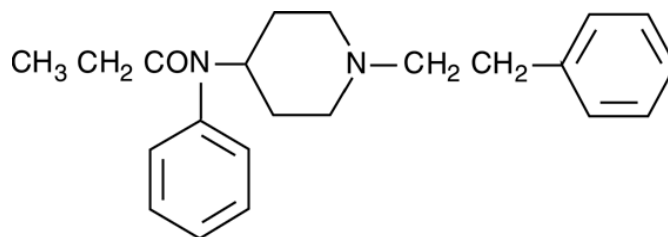
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed 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.

DURAGESIC[®] patches are intended for transdermal use (on intact skin) only. Do not use a DURAGESIC[®] patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

Avoid exposing the DURAGESIC[®] 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 DURAGESIC[®] systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC[®] dose should be adjusted if necessary.

DESCRIPTION

DURAGESIC[®] (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-piperidiny) propanamide. The structural formula is:



The molecular weight of fentanyl base is 336.5, and the empirical formula is $C_{22}H_{28}N_2O$. 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/h per 10.5 cm²). The composition per unit area of all system sizes is identical.

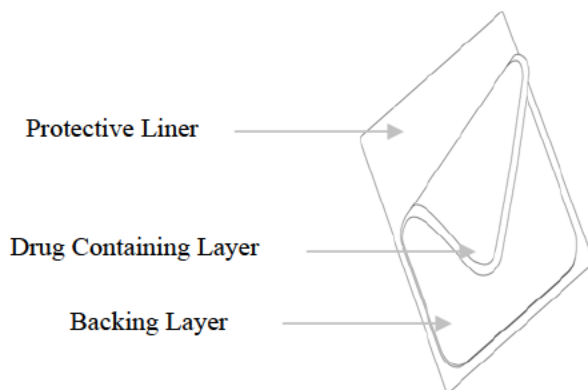
Dose* (mcg/h)	Size (cm ²)	Fentanyl Content (mg)
12**	5.25	2.1
25	10.5	4.2
50	21	8.4
75	31.5	12.6
100	42	16.8

*Nominal delivery rate per hour

**Nominal delivery rate is 12.5 mcg/hr

DURAGESIC[®] is a rectangular transparent 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/ethyl vinyl acetate film; 2) a drug-in-adhesive layer. 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 predominately 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 concentrations 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)

The DURAGESIC[®] (fentanyl transdermal system) is a drug-in-adhesive matrix designed formulation. Fentanyl is released from the matrix at a nearly constant amount per unit time. The concentration gradient existing between the 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 matrix and 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 (12.5, 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 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 20 and 72 hours after initial application (see Table A). Serum fentanyl concentrations achieved are proportional to the DURAGESIC[®] delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first two system applications. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size. Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20-27 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 3-12) hours.

Serum Fentanyl Concentrations
Following Single and Multiple Applications of DURAGESIC® 100 mcg/h

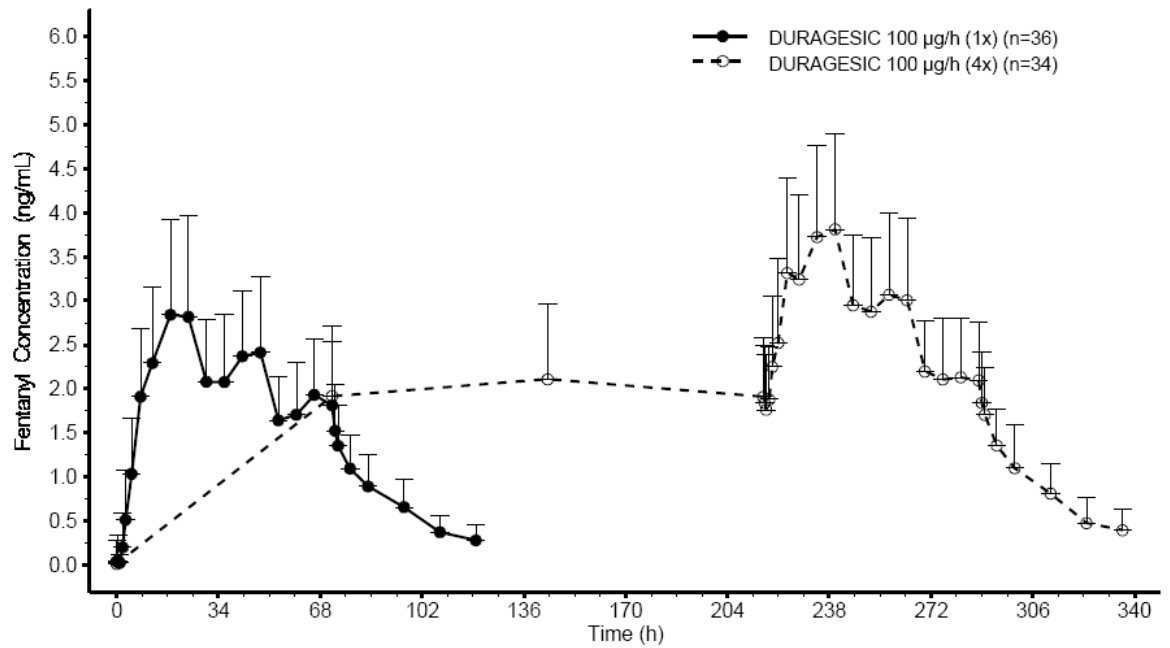


TABLE A: FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

	Mean (SD) Time to Maximal Concentration Tmax (h)	Mean (SD) Maximal Concentration Cmax (ng/mL)
DURAGESIC® 12 mcg/h	28.8 (13.7)	0.38 (0.13)*
DURAGESIC® 25 mcg/h	31.7 (16.5)	0.85 (0.26)
DURAGESIC® 50 mcg/h	32.8 (15.6)	1.72 (0.53)
DURAGESIC® 75 mcg/h	35.8 (14.1)	2.32 (0.86)
DURAGESIC® 100 mcg/h	29.9 (13.3)	3.36 (1.28)

*Cmax values dose normalized from 4 x 12.5 mcg/h

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in approximately 20-27 hours.

TABLE B: RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/h) Range [70 kg]	Volume of Distribution V_{ss} (L/kg) Range	Half-Life $t_{1/2}$ (h) Range
Surgical Patients	27 – 75	3 - 8	3 - 12
Hepatically Impaired Patients	3 - 80+	0.8 - 8+	4 - 12+
Renally Impaired Patients	30 – 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 3-8; 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 DURAGESIC® 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

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the DURAGESIC[®] fentanyl transdermal patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours.

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.

DURAGESIC[®] 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**).

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%-420%) increase in fentanyl AUC_{0-∞}. Coadministration of ritonavir in patients receiving DURAGESIC[®] 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 DURAGESIC[®]

is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce CYP3A4 activity may reduce the efficacy of DURAGESIC[®]. 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 DURAGESIC[®] 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, DURAGESIC[®] 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 DURAGESIC[®], 13 patients experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO₂ 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, post-marketing reports have been received that describe opioid-naïve post-operative patients who have experienced clinically significant hypoventilation and death with DURAGESIC[®].

While most adult and pediatric patients using DURAGESIC[®] 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 DURAGESIC[®]. The use of DURAGESIC[®] is contraindicated in patients who are not tolerant to opioid therapy.

The use of DURAGESIC[®] should be monitored by clinical evaluation, especially within the initial 24-72 hours when serum concentrations from the initial patch will

peak, and following increases in dosage. DURAGESIC[®] 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 DURAGESIC[®] was less than 1%.

CNS Effects

Central nervous system effects increase with increasing serum fentanyl concentrations.

INDICATIONS AND USAGE

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.

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 (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, DURAGESIC[®] 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, 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**

DURAGESIC® (fentanyl transdermal system) is contraindicated in patients who have or are suspected of having paralytic ileus.

DURAGESIC® (fentanyl transdermal system) is contraindicated in patients with known hypersensitivity to fentanyl or any components of this product.

WARNINGS

DURAGESIC[®] patches are intended for transdermal use (on intact skin) only. Do not use a DURAGESIC[®] patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

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 (see PRECAUTIONS – Pediatric Use).

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. Overestimating the DURAGESIC[®] dose when converting patients from another opioid medication can result in fatal overdose with the first dose. The mean half-life is approximately 20-27 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after DURAGESIC[®] removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations 20-27 hours after system removal.

DURAGESIC[®] 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 DURAGESIC[®] 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. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the DURAGESIC[®] system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C (104°F) due to temperature-dependent increases in fentanyl released from the system and increased skin permeability. **Patients wearing DURAGESIC[®] systems who**

develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC[®] dose should be adjusted if necessary.

Death and other serious medical problems have occurred when people were accidentally exposed to DURAGESIC[®]. Examples of accidental exposure include transfer of a DURAGESIC[®] patch 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 DURAGESIC[®] 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 DURAGESIC[®] in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

DURAGESIC[®] 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 DURAGESIC[®] especially during the initial 24-72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl continue to be absorbed from the skin for 20-27 hours or more after the patch is removed, hypoventilation may persist beyond the removal of DURAGESIC[®]. 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 DURAGESIC[®]. 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.

DURAGESIC[®] 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 pre-existing respiratory depression. In such patients, even usual therapeutic doses of DURAGESIC[®] 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, DURAGESIC[®] should be administered with caution to patients with pre-existing 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

DURAGESIC[®] should not be used in patients who may be particularly susceptible to the intracranial effects of CO₂ 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. DURAGESIC[®] should be used with caution in patients with brain tumors.

Interactions with Other CNS Depressants

The concomitant use of DURAGESIC[®] (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 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 DURAGESIC[®] 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, PRECAUTIONS, and DOSAGE AND ADMINISTRATION** for further information).

PRECAUTIONS

General

DURAGESIC[®] (fentanyl transdermal system) should not be used to initiate opioid therapy in patients who are not opioid-tolerant. Children converting to DURAGESIC[®] 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 DURAGESIC[®] was not prescribed. A considerable amount of active fentanyl remains in DURAGESIC[®] 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 DURAGESIC® 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

DURAGESIC® 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 DURAGESIC® 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 concentration 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 DURAGESIC®**).

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 DURAGESIC® 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 DURAGESIC[®] is dispensed because new information may be available.

Patients receiving DURAGESIC[®] patches should be given the following instructions by the physician:

1. Patients should be advised that DURAGESIC[®] patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.
2. Patients should be advised that each DURAGESIC[®] patch 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 DURAGESIC[®] patches 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 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.
4. Patients should be advised that DURAGESIC[®] should be applied immediately upon removal from the sealed pouch and after removal of the protective liner. Additionally the patient should be advised of the following:
 - The DURAGESIC[®] patch should not be used if the pouch 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 DURAGESIC[®] 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 DURAGESIC[®] 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 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[™]).
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 DURAGESIC[®] patches after removal from the skin.
11. Patients should be advised that DURAGESIC[®] may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
12. Patients should be advised to refrain from any potentially dangerous activity when starting on DURAGESIC[®] or when their dose is being adjusted, until it is established that they have not been adversely affected.

13. Patients should be advised that DURAGESIC[®] 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.
14. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with DURAGESIC[®].
15. Patients should be advised of the potential for severe constipation.
16. Patients should be advised that if they have been receiving treatment with DURAGESIC[®] and cessation of therapy is indicated, it may be appropriate to taper the DURAGESIC[®] dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
17. Patients should be advised that DURAGESIC[®] contains fentanyl, a drug with high potential for abuse.
18. Patients, family members, and caregivers should be advised to protect DURAGESIC[®] from theft or misuse in the work or home environment.
19. Patients should be instructed to keep DURAGESIC[®] in a secure place out of the reach of children due to the high risk of **fatal respiratory depression**.
20. Patients should be advised that DURAGESIC[®] 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.
21. 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.
22. When DURAGESIC[®] is no longer needed, the unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.
23. 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 DURAGESIC[®].
24. 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 DURAGESIC[®] is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce CYP3A4 activity may reduce the efficacy of DURAGESIC[®]. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfanivir, 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 fatal respiratory depression. Patients receiving DURAGESIC[®] 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 DURAGESIC[®] (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

DURAGESIC[®] 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, and Impairment of Fertility

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on AUC_{0-24h} comparison). 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 – 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 $\mu\text{g}/\text{kg}/\text{day}$) 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. DURAGESIC® 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 of 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/m² basis.

Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, DURAGESIC[®] is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore, DURAGESIC[®] is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

The safety of DURAGESIC[®] 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/h 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 DURAGESIC[®] 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 (DURAGESIC[®] plus rescue medication) was provided by DURAGESIC[®].

DURAGESIC[®] was not studied 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 (see **DOSAGE AND ADMINISTRATION** and **BOX WARNING**).

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

Geriatric Use

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the DURAGESIC[®] fentanyl transdermal patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours.

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.

DURAGESIC[®] 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 post-marketing experience, deaths from hypoventilation due to use of DURAGESIC[®] (fentanyl transdermal system) have been reported (see BOX WARNING and CONTRAINDICATIONS).

Pre-Marketing Clinical Trial Experience

Although DURAGESIC[®] use in post-operative or acute pain and in patients who are not opioid-tolerant is CONTRAINDICATED, the safety of DURAGESIC[®] 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 DURAGESIC[®] use varied in cancer patients; 56% of patients used DURAGESIC[®] for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC[®] 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-naïve patients.

Various adverse events were reported; a causal relationship to DURAGESIC[®] was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received DURAGESIC[®]. 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 DURAGESIC[®] has been evaluated in 291 patients with chronic pain 2-18 years of age. The duration of DURAGESIC[®] use varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16-30 days; 16% for 31-60 days; and 17% for at least 61 days. Twenty-five patients were treated with DURAGESIC[®] for at least 4 months and 9 patients for more than 9 months.

There was no apparent pediatric-specific risk associated with DURAGESIC[®] 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*	Dyspnea, respiratory

	hemoptysis, pharyngitis*, hiccups, bronchitis, rhinitis, sinusitis, upper respiratory tract infection*	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% - 10% of DURAGESIC® patients

**Reactions occurring in 10% or more of DURAGESIC® 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

Post-Marketing Experience - Adults

The following adverse reactions have been reported in association with the use of DURAGESIC® and not reported in the pre-marketing 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

DURAGESIC® 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 (DURAGESIC®) 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 DURAGESIC[®] 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.

DURAGESIC[®] patches are intended for transdermal use (to be applied on the skin) only. Do not use a DURAGESIC[®] patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

OVERDOSAGE

Clinical Presentation

The manifestations of fentanyl overdose 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 DURAGESIC[®] (fentanyl transdermal system) 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

DURAGESIC[®] 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 (DURAGESIC[®]) may be a particular target for abuse and diversion.

DURAGESIC[®] patches are intended for transdermal use (on intact skin) only. The DURAGESIC[®] patch should not be used if the pouch seal is broken, or the patch is cut, damaged, or changed in any way.

Each DURAGESIC[®] patch 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 DURAGESIC[®] patch occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlaid with a transparent adhesive film dressing (e.g., Bioclusive[™] or Tegaderm[™]).

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.

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. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean half-life of approximately 20-27 hours, 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 DURAGESIC® 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 DURAGESIC® 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 PRECAUTIONS for further information).

Pediatric patients converting to DURAGESIC® with a 25 mcg/h 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.

DURAGESIC® 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

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

- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

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 oral hydromorphone daily, or an equianalgesic dose of another opioid.

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 outpatient 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 DURAGESIC® 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 (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 pre-existing opioid-tolerance (see **BOX WARNING** and **CONTRAINDICATIONS**). Initial doses should be reduced in elderly or debilitated patients (see **PRECAUTIONS**).

DURAGESIC[®] (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 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 use if the pouch 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.

DURAGESIC[®] 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 pouches, 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 DURAGESIC[®] application. Reduced doses of DURAGESIC[®] are suggested for the elderly and other groups discussed in PRECAUTIONS.

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.

In selecting an initial DURAGESIC[®] 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 DURAGESIC[®] 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 DURAGESIC® Dose Selection

Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean half-life of approximately 20-27 hours, 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 systematic evaluation of DURAGESIC® as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC® from other narcotics. The efficacy of DURAGESIC® 12 mcg/h as an initiating dose has not been determined. In addition, patients who are not opioid-tolerant have experienced hypoventilation and death during use of DURAGESIC®. Therefore, DURAGESIC® should be used only in patients who are opioid-tolerant.

To convert adult and pediatric patients from oral or parenteral opioids to DURAGESIC®, 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 DURAGESIC® dose. Use this table to find the calculated 24-hour morphine dose and the corresponding DURAGESIC® dose. Initiate DURAGESIC® 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 DURAGESIC® 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/h, multiple systems may be used.

TABLE C¹: DOSE CONVERSION GUIDELINES

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

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 DURAGESIC[®] to other therapies because this conversion to DURAGESIC[®] 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 DURAGESIC[®]).**

TABLE D^{1a}: 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 DURAGESIC[®] to other therapies because this conversion to DURAGESIC[®] 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 DURAGESIC[®]).**

- 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 E¹: RECOMMENDED INITIAL DURAGESIC[®] DOSE
BASED UPON DAILY ORAL MORPHINE DOSE**

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

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC[®].

¹**Table E should not be used to convert from DURAGESIC[®] to other therapies because this conversion to DURAGESIC[®] 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 DURAGESIC[®]).**

The majority of patients are adequately maintained with DURAGESIC[®] 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 DURAGESIC[®] 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 DURAGESIC[®] cannot be made before 24 hours of wearing. The initial DURAGESIC[®] dose may be increased after 3 days (see **DOSAGE AND ADMINISTRATION - Dose Titration**).

During the initial application of DURAGESIC[®], patients should use short-acting analgesics as needed until analgesic efficacy with DURAGESIC[®] is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for “breakthrough” pain.

Dose Titration

The recommended initial DURAGESIC[®] 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 DURAGESIC[®]. The initial DURAGESIC[®] dose 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 DURAGESIC[®] 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/h increase in DURAGESIC[®] dose. DURAGESIC[®]-12 delivers 12.5 mcg/h of fentanyl.

Discontinuation of DURAGESIC[®]

To convert patients to another opioid, remove DURAGESIC[®] 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 DURAGESIC[®] to other therapies. Because the conversion to DURAGESIC[®] 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

DURAGESIC[®] (fentanyl transdermal system) is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC [®] Dose (mcg/h)	System Size (cm ²)	Fentanyl Content (mg)	NDC Number
DURAGESIC [®] -12	5.25	2.1	50458-090-05
DURAGESIC [®] -25	10.5	4.2	50458-091-05
DURAGESIC [®] -50	21	8.4	50458-092-05
DURAGESIC [®] -75	31.5	12.6	50458-093-05
DURAGESIC [®] -100	42	16.8	50458-094-05

Safety and Handling

DURAGESIC[®] is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. Do not use a DURAGESIC[®] patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

KEEP DURAGESIC[®] OUT OF THE REACH OF CHILDREN AND PETS.

Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). Apply immediately after removal from individually sealed pouch. Do not use if the pouch seal is broken. **For transdermal use only.**

Bioclusive[™] is a trademark of Ethicon, Inc.
Tegaderm[™] is a trademark of 3M

A schedule CII narcotic. DEA order form required.

Manufactured by:

ALZA Corporation
Vacaville, CA 95688

Manufactured for:

PriCara[®], Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869
Insert new code

Revised July 2009

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MEDICATION GUIDE

DURAGESIC® (Dur-ah-GEE-zik) (FENTANYL TRANSDERMAL SYSTEM)

IMPORTANT:

- Keep DURAGESIC® 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 DURAGESIC®, get emergency help right away.
- Make sure you read the separate **“Instructions for Applying a DURAGESIC® Patch.”** Always use a DURAGESIC® Patch the right way. DURAGESIC® can cause serious breathing problems and death, especially if it is used the wrong way.
- DURAGESIC® is a federally controlled substance (C-II) because it can be abused. Keep DURAGESIC® in a safe place to prevent theft. Selling or giving away DURAGESIC® 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 DURAGESIC® 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 DURAGESIC®. Do not use DURAGESIC® unless you understand everything. Talk to your healthcare provider if you have questions.

What is the most important information I should know about DURAGESIC®?

DURAGESIC® 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

DURAGESIC® 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 DURAGESIC®:

- 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 DURAGESIC® patch 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.

DURAGESIC® patch 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. DURAGESIC® 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 DURAGESIC®. Your doctor will tell you if it is safe to take other medicines while you are using DURAGESIC®.

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

How should I use DURAGESIC®?

Read the separate “Instructions for Applying a DURAGESIC® Patch”.

• **You must always use DURAGESIC® patches the right way:**

- **Do not** use a DURAGESIC® patch if the pouch 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 DURAGESIC® patch.
- **Do not** take hot baths or sunbathe while wearing a DURAGESIC® patch.

• **If you have problems with the DURAGESIC® patch 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™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a DURAGESIC® patch with any other bandage or tape.**

• **If your DURAGESIC® patch 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 DURAGESIC® more often than prescribed. Call your doctor if your pain is not well controlled while using DURAGESIC®.

• **Do not stop using DURAGESIC® suddenly.** Stopping DURAGESIC® suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). Your body can develop a physical dependence on DURAGESIC®. If

your doctor decides you no longer need DURAGESIC®, ask how to slowly reduce this medicine so you don’t have withdrawal symptoms. Do not stop taking DURAGESIC® without talking to your doctor.

• **Do not wear more than one DURAGESIC® patch 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 DURAGESIC® to pass into your body.

• **If you use more DURAGESIC® than your doctor has prescribed, get emergency medical help right away.**

• **Do not drink any alcohol while using DURAGESIC®.** 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 DURAGESIC® affects you. DURAGESIC® can make you sleepy. Ask your doctor to tell you when it is okay to do these activities.

• When you remove your DURAGESIC® patch, fold the sticky sides of a used DURAGESIC® patch together and flush it down the toilet. **Do not put used DURAGESIC® patches in a trash can.**

What are the possible side effects of DURAGESIC®?

Serious side effects include:

• **Life-threatening breathing problems.** See “What is the most important information I should know about DURAGESIC®?”

• **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 DURAGESIC® 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 DURAGESIC®.

Talk to your doctor about any side effect that

concerns you.

These are not all the possible side effects of DURAGESIC®. 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 DURAGESIC®?

- Store in original unopened pouch at room temperature.
- Keep a DURAGESIC® patch in its protective pouch until you are ready to use it.
- **Keep DURAGESIC® in a safe place out of the reach of children and pets.**
- Dispose of DURAGESIC® patches you no longer need. Open the unused packages, fold the sticky sides of the patches together, and flush them down the toilet.

General information about the safe and effective use of DURAGESIC®

- Do not use DURAGESIC® for a condition for which it was not prescribed.
- **Do not give DURAGESIC® to other people, even if they have the same symptoms you have. DURAGESIC® can harm other people and even cause death. Sharing DURAGESIC® is against the law.**

This Medication Guide summarizes the most important information about DURAGESIC®. If you would like more information, talk with your

doctor. You can ask your doctor or pharmacist for information about DURAGESIC® that is written for doctors.

For questions about DURAGESIC®, call the Ortho-McNeil Janssen Scientific Affairs Customer Communications Center at 1-800-526-7736. If this is a medical emergency, please call 911.

What are the ingredients of DURAGESIC®?

Active Ingredient: fentanyl

Inactive ingredients: polyester/ethyl vinyl acetate film backing, polyacrylate adhesive.

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

Bioclusive™ is a trademark of Ethicon, Inc.
Tegaderm™ is a trademark of 3M

Manufactured by:
ALZA Corporation
Vacaville, CA 95688

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen
Pharmaceuticals, Inc.
Raritan, NJ 08869

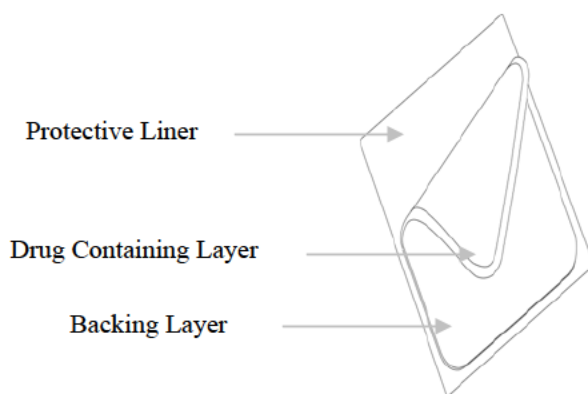
Insert New Code

July 2009

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2009

**DURAGESIC® (Dur-ah-GEE-zik)
(fentanyl transdermal system) CII**

Instructions for Applying a DURAGESIC® patch



Before Applying DURAGESIC®

- Each DURAGESIC® patch is sealed in its own protective pouch. Do not remove a DURAGESIC® patch from the pouch until you are ready to use it.
- Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged or changed in any way.
- DURAGESIC® patches are available in 5 different doses and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.

Applying a DURAGESIC® Patch

1. Skin Areas Where the DURAGESIC® Patch 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 1-4).

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.

For adults and children

- Do not put a DURAGESIC® patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- 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).
- **Talk to your doctor if you have questions about skin application sites.**

2. Prepare to Apply a DURAGESIC® Patch:

- Choose the time of day that is best for you to apply DURAGESIC®. 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 DURAGESIC® patch at a time unless your doctor tells you to do so. Before putting on a new DURAGESIC® patch, 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. Open the Pouch: Fold and tear at slit, or cut at slit taking

Figure 1



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6

care so as not to cut the patch, and remove the DURAGESIC[®] patch. Each DURAGESIC[®] patch is sealed in its own protective pouch. Do not remove the DURAGESIC[®] patch from the pouch until you are ready to use it (see Figure 6).



- 4. Peel:** Peel off both parts of the protective liner from the patch. Each DURAGESIC[®] patch has a clear plastic backing that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this backing off. Throw the clear plastic backing away. **Touch the sticky side of the DURAGESIC[®] patch as little as possible** (see Figure 7).

Figure 7



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 8). Make sure it sticks well, especially at the edges.

Figure 8



- DURAGESIC® 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 DURAGESIC® Patch).
 - 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™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a DURAGESIC® patch with any other bandage or tape.** Remove the backing from the Bioclusive™ or Tegaderm™ dressing and place it carefully over the DURAGESIC® patch, 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 DURAGESIC® patch) 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

DURAGESIC[®] patch.

7. Remove a DURAGESIC[®] patch after wearing it for 3 days (72 hours) (see “Disposing a DURAGESIC[®] Patch”).

Choose a **different** place on the skin to apply a new DURAGESIC[®] patch and repeat Steps 2 through 6.

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

Water and DURAGESIC[®]

8. You can bathe, swim or shower while you are wearing a DURAGESIC[®] patch. If the patch falls off before 3 days (72 hours) after application, discard it properly (see Disposing a DURAGESIC[®] Patch) 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 DURAGESIC[®] Patch

- Fold the used DURAGESIC[®] patch in half so that the sticky side sticks to itself (Figure 9). **Flush the used DURAGESIC[®] down the toilet right away** (Figure 10). **A used DURAGESIC[®] patch CAN be VERY dangerous for or even lead to death in babies, children, pets, and adults who have not been prescribed DURAGESIC[®].**
- Throw away any DURAGESIC[®] patches that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch 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 pouch or the protective liner down the toilet. These items can be thrown away in a trashcan.

Figure 9



Figure 10



Bioclusive[™] is a trademark of Ethicon, Inc.

Tegaderm™ is a trademark of 3M

Rx Only

Manufactured by:
ALZA Corporation
Vacaville, CA 95688

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

July 2009 Insert new code

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 29, 2009
From	Ellen Fields, M.D., M.P.H., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 19-813/SCF-044 Prior Approval CMC Supp.
Applicant	Ortho-McNeil-Janssen Pharm/J & J
Date of Submission	January 30, 2009
PDUFA Goal Date	July 30, 2009
Proprietary Name / Established (USAN) names	Duragesic/Fentanyl transdermal system
Dosage forms / Strength	Transdermal patch/ 12.5mcg/h, 50mcg/h, 75mcg/h, 100mcg/h
Proposed Indication	Management persistent, moderate-to-severe chronic pain
Recommended:	Approval

1. Introduction

Ortho-McNeil-Janssen Pharmaceuticals, Inc. on behalf of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&J) submitted a CMC prior approval supplement for Duragesic, NDA 19-813 on January 30, 2009 to change the formulation of Duragesic from a reservoir transdermal system to a matrix transdermal system.

Johnson & Johnson has marketed a transdermal fentanyl matrix system (D-TRANS) outside the United States since 2004, under the international trade name DUROGESIC. They are seeking approval of the D-TRANS matrix system as a replacement for the Duragesic reservoir transdermal system currently marketed in the US.

D-TRANS, developed by ALZA Corporation, is a drug in pressure-sensitive adhesive system. This design does not require a rate controlling membrane and the controlled release of fentanyl is achieved by the stratum corneum of the skin. The dosages of D-TRANS matrix system (12.5, 25, 50, 75 and 100 mcg/h) are identical to those of Duragesic.

The original PDUFA goal date for this CMC supplement was May 30, 2009, but due to the submission of a major CMC amendment within the last review month, the clock was extended two months to a PDUFA date of July 30, 2009.

2. Background

Duragesic (fentanyl transdermal system) was approved by the Agency in 1990 and is indicated for the 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.

Duragesic should be used only inpatients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic 25mcg/h. It is a transdermal patch available in dosage strengths of 12, 25, 50, 75, and 100 mcg/h. Each patch is to be worn continuously for 72 hours.

Since its approval, there have been two recalls of Duragesic, both due to manufacturing defects that resulted in leakage of fentanyl from the patch. Fentanyl leakage may be associated with increased exposure to fentanyl and overdose for both the patient and caregivers/household contacts.

The first recall, which occurred in February, 2004, was a Class 1 recall of the 75mcg/h dosage strength due to a manufacturing defect that resulted in a seal breach along the edge of the patch that resulted in leakage. The second recall was in February 2008, involving all lots of the 25mcg/hour patches, and was also due to a manufacturing defect that resulted in leakage. These patches had a sliced edge in the pouch containing the fentanyl gel. Importantly, this manufacturing defect occurred between March, 2006 and January, 2007, and was not noticed by the manufacturer until reported to them by a pharmacist in December 2007. Also, in February 2008, the generic manufacturer Actavis recalled all dosage strengths of their reservoir patch due to a "fold-over" defect" which may have caused the patches to leak.

Due to the recalls, the apparent inability of the manufacturer to guarantee manufacturing specifications, and the fact that the defects in the patch (second recall) were not detected by the manufacturer's quality control systems, the Division and CDER became increasingly concerned about the safety of reservoir fentanyl transdermal systems.

In March, 2008, discussions between the Division and J&J commenced in order to emphasize the public health impact of the manufacturing defects, and to explore the possibility of marketing the transdermal fentanyl matrix system which was being marketed outside the US, in the US, and remove the reservoir system from the US market. During a teleconference between J&J and the Division in June, 2008, the details of the submission were discussed. The Division agreed to the submission of a prior approval CMC supplement that would include the submission of all relevant pharmacokinetic and bioequivalence studies conducted by the Sponsor.

3. CMC

The CMC review team consisted of Amit Mitra, Ph.D., Pramoda Maturu, Ph.D., John Duan, Ph.D., Ramesh Raghavachari, Ph.D., James Vidra, Ph.D., Patrick Marroum, Ph.D., and Eric Duffy, Ph.D. The following is a summary of their findings.

The January 30, 2009 submission was incomplete in terms of CMC data. Numerous information requests were made of the Sponsor during the review cycle, and due to the

submission of a major CMC amendment within the final review month, the PDUFA goal date was extended two months.

The six submitted DMFs, referenced with Letters of Authorization by the Sponsor, were reviewed by Dr. Maturu and found adequate to support the proposed drug product formulation.

The drug product was reviewed by Dr. Amit Mitra. The following recommendations regarding tightening of impurity specifications are made in Dr. Mitra's review, however in Dr. Raghavachari Supervisory review, he states that since these specifications can be tightened based on batch test data, they may be fulfilled as post-marketing commitments.

- Revise the impurity (b) (4) specification in the drug product to limit the exposure to 1.5 mcg/day. Submit the revised method and its validation, if appropriate.
- Revise the (b) (4) specification to NMT (b) (4) ppm in the drug product. Submit the validation data for the revised analytical method.
- Revise the (b) (4) acceptance criterion in the drug product to limit the exposure to NMT 1.5 mcg/day. Submit the validation data for the revised analytical method.
- Develop a sensitive method to determine (b) (4) with LOD sensitive enough to determine the threshold for safety of those compounds (b) (4) ppm for (b) (4) and 1.5mcg/day for (b) (4). If present in detectable quantities, adopt a specification for those impurities in the drug product. Submit the analytical method and its validation.

Dr. John Duan reviewed bioequivalence from the CMC perspective based on *in vitro* drug release specifications and found the Sponsor's justification acceptable. All proposed manufacturing facilities have been found acceptable by the Office of Compliance. Method validation was carried out by the Office of Testing and Research in St. Louis, MO., by Dr. James Allgire. He determined that all methods were acceptable after agreement was made with the Sponsor regarding comments conveyed to them.

From the CMC perspective, the deficiencies noted by Dr. Mitra regarding (b) (4) can be resolved via post-marketing commitments, and do not preclude approval. Dr. Mellon asked the CMC team whether the methodologies employed by the Sponsor for the analysis of potential extractables/leachables are acceptable and adequate. Although Dr. Raghavachari stated in his review that these methods are scientifically acceptable, during a teleconference with the Sponsor on July 28, 2009, the CMC team requested that the Sponsor provide, as a post-marketing commitment, data to demonstrate the specificity of the assays used in the

leachable/extractable studies. The Sponsor was also requested to develop a Probe Tack test Duragesic as a post-marketing commitment.

Regarding the (b) (4) impurities that did not have reference standards, Dr. Raghavachari stated in his review that the absence of reference standards is reasonable since the compounds are (b) (4).

4. Nonclinical Pharmacology/Toxicology

Dr. Mamata De completed the primary review of the pharmacology/toxicology data submitted in support of this application and Dr. Dan Mellon completed a supervisory review of these issues. Please refer to their reviews for details; what follows is a summary.

Multiple nonclinical recommendations were given to the Sponsor during a meeting with the Division on June 19, 2008 regarding this CMC supplement. These included the submission of:

- Final study reports for all toxicology studies including comparison of formulations tested with the formulation proposed in the supplement
- Information on potential extractables and leachables from the drug product formulation including toxicological evaluation to determine the safe level of exposure
- Safety of (b) (4) novel excipient)
- Final study reports of carcinogenicity studies
- Adequate qualification for any impurity or degradation product that exceeds ICH threshold

The Sponsor submitted final study reports of a primary skin irritation assay, a 28-day repeat-dose skin irritation assay and a dermal hypersensitivity assay. These studies were reviewed by Dr. De and deemed acceptable

The original submission did not contain the previously requested extractable/leachable information on the drug product formulation, and therefore, subsequent discussions with the Sponsor were necessary in order to obtain these data. In a submission received July 2, 2009, the sponsor provided results of extractable/leachable testing with their safety assessment of the findings. Dr. De has concluded that the study designs (solvents, temperatures, duration) are acceptable in terms of the extractable/leachable conditions.

The drug substance specifications were found acceptable for impurities with (b) (4).

The qualification threshold for nongenotoxic drug product degradation products was NMT (b) (4) or (b) (4) mcg total daily intake, whichever was lower.

Of the fentanyl related impurities/degradants, five contain (b) (4) and (b) (4).

should be regulated at the NMT 1.5 mcg/day level. (b) (4)
(b) (4) exceeded the threshold for toxicological concern of 1.5 mcg/day.

According to Dr. Mellon's review, the following substances require the tightening (b) (4)
(b) (4) or establishment of specifications (b) (4)

(b)
(4)
(4)

(b) (4) impurities in drug product: (b) (4)

The Sponsor submitted a final study report for a 2-year rat bioassay for carcinogenicity which was reviewed by Drs. Steve Leshin and Adam Wasserman, and presented to the Executive Carcinogenicity Assessment Committee. The study was deemed valid and the results were negative.

Findings of the nonclinical review do not preclude approval of this supplement; however post-marketing commitments are necessary to address outstanding concerns regarding several potential drug product impurities. Dr. Mellon put forth the following recommendations for nonclinical studies:

1. Due to the incomplete genetic toxicology characterization and the prediction of clastogenicity for Impurity B via the FDA Computational Toxicology structure activity analysis, the sponsor should reduce the drug product specification for fentanyl impurity B to NMT (b) (4) % in order to keep the exposure to NMT 1.5 mcg/day or conduct an in vitro assay to characterize the clastogenic potential of Impurity B that demonstrates a lack of genotoxicity.
2. Reduce the levels of (b) (4) in the drug product to less than 1.5 mcg/day (b) (4) ppm) or improve the sensitivity of the analytical technique to clearly demonstrate that the levels of the impurity do not exceed 1.5 mcg/day.
3. Reduce the specification for (b) (4) to NMT (b) (4) ppm. Although the data to date suggest that (b) (4) is a possible human carcinogen, the effect does not appear to be due to direct mutagenicity and therefore a threshold should exist. Based upon the published no-adverse-effect of (b) (4) ppm via inhalation, the proposed specification of NMT (b) (4) ppm should be tightened to NMT (b) (4) ppm.
4. Due to a lack of assay sensitivity, the theoretical exposure to (b) (4) may exceed the threshold for toxicological concern (NMT 1.5 mcg/day) and there are inadequate data regarding the genotoxic potential of this compound. The Sponsor should improve the sensitivity of their assay for this potential impurity to determine if it is present in the patch leachate at levels that would result if exposure that could exceed 1.5 mcg/day, or conduct an in vitro assay to characterize the

clastogenic potential of (b) (4) that demonstrates a lack of genotoxicity.

Dr. Mellon also noted in his review, that (b) (4) was identified as a possible minor byproduct of (b) (4) breakdown. There is limited data on the potential toxicity of (b) (4) but it is known to form (b) (4) the body. (b) (4) was not able to be quantified by J&J in any of the extractable solutions, and could not be detected in placebo patches at a limit of detection of (b) (4) ppm. The sensitivity of the assay methodology was discussed with the Sponsor during a telecon held July 28, 2009, and was determined to be adequate by the CMC team. According to Dr. Mellon, the level of (b) (4) if present at all, is likely around the (b) (4) ppm levels set by NIOSH. Given the high volatility of this chemical, the sensitivity of the assays employed to date, and the (b) (4) presence of (b) (4), there do not appear to be any safety concerns due to the potential presence of (b) (4). No further studies are required.

The last approved label for Duragesic was updated to include the results of the carcinogenicity study.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was performed by Rajanikanth Madabushi, Ph.D., with secondary concurrence from Suresh Doddapaneni, Ph.D. The following is a brief summary of the review.

The clinical pharmacology and biopharmaceutics program performed to support the approval of the D-TRANS matrix formulation included the following studies that were reviewed Dr. Madabushi:

- A pivotal bioequivalence study, conducted to evaluate the pharmacokinetics of the D-TRANS fentanyl matrix system with the approved US DURAGESIC fentanyl reservoir system at the highest marketed dose strength of 100 mcg/h.
- A pharmacokinetic study to evaluate the pharmacokinetics of fentanyl following single and repeated application of D-TRANS.
- A dose proportionality study of D-TRANS over the range of 25 mcg/h - 100 mcg/h.
- Studies to characterize the effect of age, skin types, site of application and application of external heat on fentanyl pharmacokinetics.

The key clinical pharmacology and biopharmaceutics findings are:

- The 100 mcg/h D-TRANS matrix system is bioequivalent to the 100 mcg/h DURAGESIC fentanyl reservoir system.
- The pharmacokinetics of fentanyl does not change upon the repeated application of D-TRANS matrix system. Upon repeated application, there is ~40% accumulation of fentanyl exposure. Steady-state is most likely reached by the end of second consecutive dose.
- The systemic exposures (serum AUC and Cmax) of fentanyl after application of the D-TRANS matrix system increased in a dose proportional manner over the range of 25mcg/h to 100 mcg/h.

- The D-TRANS matrix system is associated with less variability compared to DURAGESIC reservoir system and random spiking in serum fentanyl concentrations is not seen with D-TRANS matrix system over the range of 25 mcg/h to 100 mcg/h dose strengths.
- The effect of heat is similar for both DURAGESIC and D-TRANS matrix system throughout the duration of the application. The initial application of heat (0 to 10 hours) significantly increased serum fentanyl concentrations for both DURAGESIC (C_{10} and AUC(0-10) by 81% and 184%) and D-TRANS matrix system (C_{10} and AUC(0-10) by 61% and 120%). The effect was comparatively minimal (less than 26 % for both formulations) with the second application of heat between 26 – 36 h.
- The D-TRANS matrix has a better adhesion compared to Duragesic over the duration of the 72-hr wearing period. Further, the adhesion characteristics are not significantly affected by repeated application, heat and skin type by African descent or geriatrics.

The Office of Clinical Pharmacology determined that the clinical pharmacology data submitted in support of this supplement is acceptable and does not preclude approval.

6. Efficacy

There were no efficacy studies submitted with this application.

7. Safety

The safety of D-Trans Matrix has been assessed using two sources from this submission; the dermatologic safety studies, and the Sponsor's integrated summary of safety that includes post-marketing data.

Dermal Safety Studies

Two dermal safety studies were submitted as part of the sNDA. DAARP consulted the Division of Dermatology and Dental Products (DDDP) to evaluate the adequacy of the two studies. The product used in the dermal safety studies was D-TRANS, which is identical to the proposed Duragesic Matrix product in this application. Dr. Snezana Trajkovic (DDDP) performed the review of the submitted studies with concurrence from Dr. David Kettl, Clinical Team Leader, and Dr. Susan Walker, Division Director, DDDP. The following summarizes the consult response from DDDP. Please refer to Dr. Trajkovic's review for further details.

The Sponsor had previously submitted two protocols to the Agency for evaluation, and comments from DDDP were provided to the Sponsor in April, 2001. However, the studies appear to have been conducted without the suggested amendments.

Trial C-2002-053-02 was a single-center, randomized, double-blind study to evaluate phototoxic potential of DTRANS fentanyl matrix system in healthy adult subjects that enrolled 38 healthy male and female subjects 18 to 45 years of age.

Details regarding the study design are discussed in Dr. Trajkovic's review. Of note, the dose of fentanyl in the D-TRANS systems was 2.4mcg/h. The lowest to-be-marketed dose is 25mcg/h. Placebo and active patches were applied for 24-hours.

Topical reactions were scored using scales measuring the extent and severity of erythema, papules, and edema. A dermatologist examined the skin site within 24 hours of any severe reaction. Additionally, adherence of each D-TRANS system was assessed before the system was removed using a 5-point scale that ranged from 90% adherence to no adherence.

DDDP's conclusions regarding this trial are the following:

- Phototoxicity did not occur during the conduct of this study, however this finding is (b) (4) because the dose of the active drug, 2.4 mcg/h, was significantly lower than the to-be-marketed product, and lower than the 25mcg/h recommended by DDDP in their earlier consult response.
- Adverse events reported were related to systemic effects of the drug product and not due to the patch product.

Trial C-2002-050-01 was a single-center, open-label study 229 healthy volunteers to evaluate contact sensitization potential of the components of D-TRANS Fentanyl matrix System 42 cm², without the drug.

Details regarding the study design are discussed in Dr. Trajkovic's review. Topical reactions were assessed, as well as adherence of the systems.

DDDP's conclusions regarding this trial are the following:

- The open-label trial design is not adequate to evaluate contact sensitization potential of the D-TRANS matrix system.
- Erythema and papules were reported in a significant number of subjects after the induction phase of the trial (54% and 46% respectively), which may represent an irritancy signal.

DDDP provided the following recommendations regarding dermal safety evaluations (from Dr. Trajkovic's review):

The applicant has not conducted dermal safety evaluations that DDDP typically recommends for topical products, and the submitted studies would not be considered to be adequate provocative dermal safety evaluations of the patch product.

However, the Division recognizes the difficulty with performing 21 day sensitization/irritation studies with the active drug containing patch, particularly in products containing opioids. If the sponsor has conducted a systematic algorithm to assess and record irritation of active fentanyl containing patches in actual use conditions during the phase 3 trials, and has sufficient international post marketing experience, then the primary review division may reasonably conclude that they have an adequate safety database for (b) (4). In this situation, the need for specific provocative dermal safety studies could be waived by the primary review division.

The results of these studies are not adequate to conclude that significant Contact Sensitization did or did not occur, since the open label nature of the study could incorporate observer bias. (Trial C-202-050-01)

Phototoxicity did not occur during conduct of dermal safety studies with the product, but this finding is (b) (4). (Trial C-202-053-02)

However, during the conduct of trial C-2002-050-01 an irritancy signal was noted. Therefore, if the phase 3 trial data in combination with the post marketing safety experience is deemed adequate for labeling, additional studies for topical safety may not be necessary. If the safety database is deemed not adequate, then a Cumulative Irritancy/Sensitization trial is recommended to support of the dermal safety of the sponsor's product. Additionally, DDDP recommends that Photoallergenicity study be conducted in order to complete dermal safety evaluation of the product.

Integrated Summary of Safety

The Summary of Clinical Safety presents safety data from the following sources:

- A pivotal bioequivalence study (FEN-PAI-1019) conducted to establish bioequivalence between the D-TRANS matrix system (100 µg/h) and the DURAGESIC reservoir system (100 µg/h);
- A bioequivalence study (C-2003-038) that established bioequivalence between 4 x 12.5 µg/h D TRANS matrix systems and 1 x 50 µg/h D TRANS matrix system and between 4 x 12.5 µg/h D TRANS and 2 x 25 µg/h DUROGESIC reservoir systems;
- Study C-2004-005 that investigated the effects of external heat on the pharmacokinetics during the applications of both reservoir and matrix systems;
- The Summary of Clinical Safety that supported the initial Marketing Authorization Application (MAA) of the D-TRANS fentanyl matrix system in the European Union (EU). The Summary included pooled data from 5 studies conducted in 223 healthy volunteers and data from 2 additional studies that addressed specific topical safety issues (sensitization and phototoxicity potential)
- Postmarketing reports: adverse events (AEs) that have been reported with the use of fentanyl transdermal reservoir and matrix systems collected cumulatively from 01 April 2004 through 30 September 2008 and are provided.

All of the studies submitted in support of this application were conducted in healthy volunteers who were treated with naltrexone in order to block systemic opioid effects. Consequently, the adverse events other than application site reactions reported from these studies may not be representative of events that occur in patients treated for the labeled indications. However, the systemic effects of fentanyl have been well characterized. Therefore, the utility of this summary is in the assessment of application site reactions. The post-marketing reports provide some information regarding systemic adverse events associated with the use of the D-TRANS Matrix system.

Exposure:

A total of 575 healthy subjects were exposed to at least one application of D-TRANS Matrix System. The majority of subjects enrolled in were Caucasian males below age 50. The longest duration of exposure to D-TRANS was 15 days. Doses to which subjects were exposed included 25mcg/h, 50mcg/h, 75mcg/h, and 100mcg/h.

Adverse Events:

There were no deaths reported, and only one serious adverse event of hematemesis following an initial dose of naltrexone.

The case of hematemesis occurred in a 21-year old female patient following the administration of the first 50 mg dose of naltrexone (~ 14 hours prior to D-TRANS application) in Period 2 of Study C-2003-038 (BE study comparing 4 x 12.5 mcg/h D-TRANS with 1 x 50 mcg/h and 2 x 25 mcg/h). The subject's previous D-TRANS application had been 12 days prior to this dose of naltrexone. Approximately one hour after the dose of naltrexone was administered, the subject developed nausea, tremor, and abdominal pain which were mild. One hour later she developed mild hematemesis (2 instances of vomiting with ~15 cc fresh blood total). This adverse event is likely related to the administration of naltrexone. Since it was not temporally associated with the application of D-TRANS, there is little chance of any association of the hematemesis with D-TRANS fentanyl.

Overall, 11 subjects discontinued the studies due to AEs, which included vomiting, nausea, erythematous/purpuric rash, upper respiratory tract infection, hematemesis, rhinitis, headache, and sty on eyelid. All events were mild to moderate in intensity. The majority of AEs were of mild severity, and in all studies, the systemic and topical safety profiles were comparable between treatment groups. The most common AEs reported were vomiting, headache, and nausea, which are known adverse reactions associated with both fentanyl and naltrexone.

The majority of adverse events were of mild severity, and in all studies, the systemic and topical safety profiles were comparable between treatment groups. The most common adverse events included vomiting, nausea, and headache. The rates of these events were similar between the Duragesic reservoir and D-TRANS Matrix treatment groups. There was no relationship between the incidence of AEs and the dose of D-TRANS.

No new safety issues were identified with any treatment, and adverse events reported with the use of D-TRANS matrix system were consistent with the events reported with DUROGESIC and DURAGESIC reservoir systems with respect to characteristics and severity.

Application Site Reactions/Topical Adverse Events:

The most common adverse skin reactions were erythema, itching, pruritus, and rash. All were considered treatment related, and most were mild in severity; none were severe. The majority of topical reactions resolved within 24-hours after removal of the system. One subject developed a mild pustular rash one hour after removal D-TRANS 50mcg/h that persisted 14 days and was felt to be treatment related. The proportion of reactions was similar between those receiving D-TRANS and Durogesic (reservoir system) as shown in the table below.

The following table from the submission shows the number and percentage of subjects reporting application site reactions by study. The pooled data in this table includes five clinical studies (223 healthy volunteers) that were used to support the Marketing Authorization Application (MAA) of D-TRANS in the European Union (EU).

Summary of Subjects [Number (%)] Reporting Application Site Reactions by Study

Body System COSTART Term	Study C2002-046		Study C2002-047		Study C2002-049	
	Durogesic 100 µg/h(2X) (n=37)	D-TRANS 100 µg/h(2X) (n=37)	D-TRANS 100 µg/h(1X) (n=36)	D-TRANS 100 µg/h(4X) (n=34)	Durogesic 100 µg/h(4X) (n=39)	D-TRANS 100 µg/h(4X) (n=42)
Subjects reporting at least one application site reaction	11 (29.7)	5 (13.5)	5 (13.9)	7 (20.6)	4 (10.3)	4 (9.5)
Body as a Whole	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Extremity pain	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Skin System	11 (29.7)	5 (13.5)	5 (13.9)	7 (20.6)	4 (10.3)	4 (9.5)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
Infection/Inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
Itching	2 (5.4)	1 (2.7)	5 (13.9)	7 (20.6)	3 (7.7)	3 (7.1)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Pruritus	9 (24.3)	4 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: Results were based on data collected from 5 clinical studies: 'D-TRANS Fentanyl' studies include C2002046, C2002047, C2002048, C2002049, and C2002052. 'Durogesic' studies include C2002046 and C2002049. A subject may be reported in more than one COSTART/body system category and in more than one treatment group. 1X=1 system, 2X=2 nonconsecutive systems, 4X=4 consecutive systems

Summary of Subjects [Number (%)] Reporting Application Site Reactions by Study

Body System COSTART Term	Study C2002-048				Study C2002-052
	D-TRANS 25 µg/h(1X) (n=33)	D-TRANS 50 µg/h(1X) (n=32)	D-TRANS 75 µg/h(1X) (n=33)	D-TRANS 100 µg/h(1X) (n=31)	D-TRANS 100 µg/h(1X) (n=71)
Subjects reporting at least one application site reaction	1 (3.0)	0 (0.0)	3 (9.1)	2 (6.5)	0 (0.0)
Body as a Whole	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Extremity pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin System	1 (3.0)	0 (0.0)	3 (9.1)	2 (6.5)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection/Inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Itching	1 (3.0)	0 (0.0)	1 (3.0)	1 (3.2)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	2 (6.1)	1 (3.2)	0 (0.0)

The proportion of subjects reporting application site reactions ranged from zero to 20% for those exposed to D-TRANS, and from 10% to 30% to those exposed to Durogesic reservoir system in the five pooled studies. The most common reactions were pruritus and itching which were equivalent across treatment groups.

Post-marketing reports

The Sponsor provided the cumulative adverse events that have been reported with the use of fentanyl transdermal reservoir and matrix systems and received by Strategic Clinical and Epidemiological Pharmacovigilance Technology for Risk Evaluation (SCEPTRE) from April, 2004 through September, 2008. This represents the time period that both the reservoir and matrix systems have been marketed in various parts of the world.

The SCEPTRE search resulted in 11, 496 cases that reported the use of reservoir, matrix, and/or an unspecified transdermal system. Sixty-four percent of the reported exposure was for the reservoir system, and the greatest proportion of cases were from the US, Japan, and Germany.

Overall, the most frequently reported preferred terms (PTs) were drug ineffective, nausea, and pharmaceutical product complaint. For both the reservoir and matrix systems, the reported PTs comprised expected opioid-related events, such as nausea, vomiting, somnolence, events related to drug withdrawal or lack of efficacy, central nervous system (CNS)-related events, and overdose. Also reported were application site reactions.

The percentage of fatal cases for all systems combined was 21%; the percentages of fatal cases were 24% and 3% for the reservoir and matrix systems, respectively. The reason for this imbalance is not clear. The Sponsor cites a possible explanation related to differences in reporting rates between the U.S. and outside the U.S, and the solicited reporting of deaths from the US patient assistance program.

Physical dependence and withdrawal, convulsions, disorientation, euphoria and excitability, sedation, hypotension, decreased gastrointestinal motility/constipation, and urinary retention were reported in similar percentages of reservoir and matrix system AE

cases. The highest percentage was for sedation, which was reported in 9% of the reservoir system AE cases and 6% of the matrix system AEs.

Of the risks of interest from the DURAGESIC Risk Management Plan, addiction, accidental exposure, device failure, diversion, drug abuse, intentional misuse, off label use and respiratory depression were reported in <5% of AE cases, both overall and for each system type.

Of the other risks of interest from, medication errors accounted for 10% of the AE cases reported with all transdermal systems. The percentages were similar for the reservoir (9%) and matrix (11%) systems. Overdose accounted for 8% of the AE cases reported with all transdermal systems. The percentages were similar for the reservoir (6%) and matrix (3%) systems. Regarding the additional selected events of interest and events in special populations, drug interactions, drug exposure during pregnancy, and events in pediatric patients were reported in $\leq 2\%$ of AE cases, both overall and with either system. A total of 26% of all AE cases involved geriatric patients, with similar percentages for the reservoir (26%) and matrix (27%) systems.

Based on the review of the postmarketing safety data, the overall safety profile of fentanyl transdermal systems is consistent with what is described in the current product labeling. The only notable difference between the safety profiles of the two delivery systems appears to be a lower percentage of serious, including fatal, cases reported with the matrix system. The Sponsor states that the difference may be attributed to several factors with a potential effect on reporting for the reservoir system, including a higher reporting of an indication for cancer pain, solicited reporting of deaths from the US patient assistance program, and the advanced stage in the product lifecycle.

Safety Summary

- There do not appear to be any new or unexpected safety signals associated with D-TRANS matrix fentanyl system compared with the Durogesic/Duragesic reservoir fentanyl systems based on a review of the studies in healthy subjects and post-marketing data provided by the Sponsor.
- The proportion and types of application site reactions are similar in those exposed to D-TRANS matrix fentanyl system compared to those exposed to Durogesic reservoir fentanyl system.
- The two dermal safety studies submitted by the Sponsor were not adequately designed to provide definitive data regarding skin sensitization and irritation potential. One study did demonstrate the absence of phototoxicity, however the dose of fentanyl in the study patch was one-tenth that of the lowest to-be-marketed dose of D-TRANS, therefore (b) (4)
The Division of Dermatology and Dental Products has recommended that a 21-day cumulative irritancy/sensitivity study and a photoallergenicity study be conducted, with the caveat that the Division may defer these studies if there is

adequate data from Phase 3 trials and post-marketing reports. They acknowledge the difficulties that accompany the conduct of a 21-day study of an opioid-containing patch in healthy subjects.

- The data provided by the Sponsor appears adequate to characterize the safety of D-TRANS. The safety profile appears comparable to the reservoir fentanyl transdermal system. In terms of dermal safety, neither the post-marketing reports over a period of many years nor the studies carried out by the Sponsor in healthy subjects indicate any additional safety signals beyond those already known to be associated with both transdermal systems. It is not necessary then, for the Sponsor to conduct any additional dermal safety studies.

8 Pediatrics

There are no pediatric issues related to this CMC supplement.

9. Labeling

The last approved Duragesic label is being amended to include appropriate wording regarding the matrix formulation including and updating of the pharmacokinetic and carcinogenicity sections; wording specific to the reservoir formulation is being removed. The remainder of the label is unchanged.

10. Recommended Regulatory Action

Recommended action

Approval with post-marketing requirements and commitments to address CMC and Pharmacology/toxicology deficiencies

Post-Marketing Requirements and Commitments

The following post-marketing requirement has been conveyed to and agreed upon by the Sponsor:

1. Reduce the drug product specification for fentanyl impurity B to NMT (b) (4)% in order to keep the exposure to NMT 1.5 mcg/day or conduct an in vitro assay to characterize the clastogenic potential of Impurity B that demonstrates a lack of genotoxicity.

Sponsor requirement: to conduct an in vivo mouse micronucleus test with isolated impurity B.

Final Protocol Submission: October 1, 2009

(b) (4)

Study completion: 1 January 2010

Final Report submission: 1 March 2010

The following post-marketing commitments have been conveyed to and agreed upon by the Sponsor:

1. Reduce the levels of (b) (4) in the drug product to less than 1.5 mcg/day ((b) (4) ppm) or improve the sensitivity of the

analytical technique to clearly demonstrate that the levels of the impurity do not exceed 1.5 mcg/day.

Sponsor commitment: to attempt to reduce the limits of detection and quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

2. Reduce the specification for (b) (4) from NMT (b) (4) ppm to NMT (b) (4) ppm.

Sponsor commitment: to reduce the limit of quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of NMT (b) (4) ppm. After collection of additional batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

3. Improve the sensitivity of the assay for (b) (4) to determine if it is present in the patch leachate at levels that would result if exposure that could exceed 1.5 mcg/day, or conduct an in vitro assay to characterize the clastogenic potential of (b) (4) that demonstrates a lack of genotoxicity.

Sponsor commitment: to evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the levels of the material do not exceed 1.5 µg/day (equivalent to (b) (4) ppm in the product). The final report will be provided to the FDA by January 31, 2010.

4. Provide data to demonstrate the specificity of the methods used in the leachable/extractable studies.

Sponsor commitment: to demonstrate the specificity of the assays used in the extractable/leachable studies. The final report will be provided to the FDA by January 31, 2010.

5. Develop a Probe Tack test for Duragesic.

Sponsor commitment: to conduct the Probe Tack test and submit the test method, validation report and specification by December 31, 2009.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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/s/

ELLEN W FIELDS
07/30/2009

BOB A RAPPAPORT
07/31/2009

I have read all of the reviews of this supplement, including this review by Dr. Fields. I am in complete agreement with Dr. Fields' conclusions and concur with her recommended action of approval.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

CHEMISTRY REVIEW(S)

CMC Executive Summary:

=====	
NDA: 19-813/SCF-044	Submission Date(s): 01/30/2009
Brand Name	Duragesic®
Generic Name	Fentanyl Transdermal System
CMC Review Team:	Amit Mitra, Ph.D.
	Paromoda Maturu, Ph.D.
	John Duan, Ph.D.
	Ramesh Raghavachari, Ph. D.
	Terrance Ocheltree, Ph.D.
	James D. Vidra, Ph.D.
	Patrick Marroum, Ph.D.
	Eric Duffy, Ph.D.
Methods Validation	(b) (4)
cGMP Inspection	Compliance Team- ‘Acceptable’ recommendation for all proposed facilities
CMC Division	Division of Post-Marketing Evaluation, Br. VII
OND division	Division of Anesthesia, Analgesia and Rheumatology Products
Applicant/Sponsor	Ortho-McNeil-Janssen Pharmaceuticals Inc.,
Submission Type	Code NDA 505(b)(1); Priority (CMC Supplement)
Provides for	Transition from Reservoir Patch to Matrix Patch
Formulation	Strength(s) Transdermal Matrix Patch
Proposed Indication	Management of persistent moderate to severe pain

Regulatory History:

NDA 19-813 was originally approved on August 07, 1990 as a reservoir patch in five different strengths (12.5 µg/hr, 25 µg/hr, 50 µg/hr, 75 µg/hr, 100 µg/hr).

The currently approved drug product is a dermal patch with a drug formulation in a reservoir. The proposed change in formulation is intended to convert the reservoir patch into a matrix patch which has been marketed in Europe and Australia.

The applicant was encouraged by the Agency to submit this supplement to remove the current reservoir patch from the market due to safety reasons (refer telecom meeting minutes dated March 21, 2008 in DFS). The proposal was submitted by the applicant on May 21, 2008 for a Type A meeting on June 19, 2008 (refer to meeting minutes dated July 15, 2008 in DFS).

The supplemental submission was received in January dated 01/30/2009. This submission was found to be incomplete in many respects, from the time review of this application was assigned and executed by the team,. During the review process several requests for information was made to the applicant and several amendments were

received. Hence, the PDUFA clock was extended by two months due to the major amendments submitted by the applicant just two weeks before the PDUFA goal date.

This summary has four sections (i) DMF reviews by the chemistry reviewer, (ii) the drug product review by the dermal patch expert reviewer, (iii) bioequivalence review by the biopharmaceutical reviewer, (iv) the compliance inspection report, and (v) methods validation report from the (b) (4).

CMC Recommendations:

From CMC point of this supplement is recommended for approval provided the deficiencies are addressed by the applicant under a Phase IV commitment to be addressed within six months from the date of approval.

Review Summary:

DMFs:

Drug Master Files (DMF) were referenced with Letters of Authorization by the applicant. All of the six referenced DMFs were reviewed by Dr. Pramoda Maturu and were found to be adequate to support the proposed drug product formulation:

DMF	(b) (4)	Adequate	-Refer DARRTS 06/29/2009
DMF	(b) (4)	Adequate	-Refer DARTTS 06/29/2009
DMF	(b) (4)	Adequate	-Refer DARTTS 04/29/2009
DMF	(b) (4)	Adequate	-Refer DARRTS 07/01/2009
DMF	(b) (4)	Adequate	-Refer DARRTS 07/02/2009
DMF	(b) (4)	Adequate	-Refer DARRTS 07/08/2009

DMF encompasses the drug substance and all (b) (4) the materials that are used in the manufacturing of the drug product.

Drug Product:

Drug Product was reviewed by Dr. Amit Mitra who is a recognized FDA expert on dermal patches.

The review recommends approval and the conclusions from the review were based on several information requests during the review process and post marketing commitments.

Dr. Mitra's review has recommended approval with the following recommendations based on pharmtox related issues to the applicant:

- Revise the impurity (b) (4) specification in the drug product to limit the exposure to 1.5 mcg/day. Submit the revised method and its validation, if appropriate.
- Revise the (b) (4) specification to NMT (b) (4) ppm in the drug product. Submit the validation data for the revised analytical method.

- Revise the (b) (4) acceptance criterion in the drug product to limit the exposure to NMT 1.5 mcg/day. Submit the validation data for the revised analytical method.
- Develop a sensitive method to determine (b) (4) with LOD sensitive enough to determine the threshold for safety of those compounds (b) (4) ppm for (b) (4) and 1.5 mcg/day for (b) (4). If present in detectable quantities, adopt a specification for those impurities in the drug product. Submit the analytical method and its validation.

Comments:

The above deficiencies are related to tightening of impurities specifications and it appears these can be communicated to the applicant such that a phase IV commitment can be made as a condition of approval could be made from CMC point of view. Since these impurity specifications certainly can be tightened based on batch test data.

One of the major concerns of the Pharmtox secondary review by Dr. Dan Mellon was that the methodologies employed by the applicant for the analysis of potential extractables are sensitive enough and are acceptable and adequate. The methods employed for the potential extractables were GC-MS or GC (b) (4) or HPLC (b) (4) where applicable. The applicant has used GC /MS or GC (b) (4) in cases where the extractable is volatile and where there is no (b) (4) functionality in the molecule. In the case where the extractable is less volatile HPLC (b) (4) is employed. From a CMC scientific point of view, the analytical methods employed in the analyses of potential extractables are adequate and acceptable. The applicant stated that the potential extractables list was obtained from (b) (4) and these methods were validated for the purpose of analysis and not for routine regulatory testing. Further, the applicant states these methods are industry standards for the analysis of extractables.

Bioequivalence:

Dr. John Duan reviewed the bioequivalence based on the currently approved reservoir and the proposed matrix formulation, the in-vitro drug release specification and the justification provided using the dissolution information (review dated 05/08/2009 in DFS). The review also incorporates the justification of the rate of drug release provided for each strength based on the release test and specifications provided by the applicant. Recommendation for approval was based on his review and the additional information submitted by the applicant during the review process.

Compliance:

All the proposed facilities propose for the manufacturing of the drug product and the testing laboratories have been found 'acceptable' by the Office of Compliance for the three facilities listed in the application (EES dated 05/26/2009).

Comments:

The comments from the (b) (4) were communicated to the applicant. The applicant has agreed to implement the recommendations from the (b) (4) methods validation procedures.

Conclusions and Recommendations:

The application still appears to have deficiencies based on the review by Dr. Mitra and the Pharmtox recommendations due to the impurities from the adhesive and the extractable and leachable data. From CMC point of view these deficiencies can be under a phase IV commitment from the applicant as a condition of approval. The application is recommended for approval depending upon the risk assessed over the benefits as determined by the Division Director.

The labeling on the patch itself should read as 'Duragesic' and not 'D-TRANS System'. Since there is no such drug product with that name has been approved by the Agency.

With the help of Pharmacology/Toxicology Team leader Dr. Dan Mellon, these issues were communicated to the applicant on 07/28/2009. The applicant agreed to change the specifications based on batch test data or perform appropriate studies per pharmtox requirements. The sensitivity of the test methods used in the above studies would also be determined. Agency expects that these Phase IV commitments to be fulfilled within a period of six months from the date of approval of this supplemental NDA.

From CMC point of this supplement is recommended for approval provided the deficiencies are addressed by the applicant under a Phase IV commitment to be addressed within six months from the date of approval.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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/s/

RAMESH RAGHAVACHARI
07/30/2009
Executive summary for CMC reviews

JAMES D VIDRA
07/30/2009

ERIC P DUFFY
07/30/2009

CMC Executive Summary:

NDA: 19-813/SCF-044	Submission Date(s): 01/30/2009
Brand Name	Duragesic®
Generic Name	Fentanyl Transdermal System
CMC Review Team:	Amit Mitra, Ph.D. Paromoda Maturu, Ph.D. John Duan, Ph.D. Ramesh Raghavachari, Ph. D. Terrance Ocheltree, Ph.D. James D. Vidra, Ph.D. Patrick Marroum, Ph.D. Eric Duffy, Ph.D.
Methods Validation	(b) (4)
cGMP Inspection	Compliance Team- 'Acceptable' recommendation for all proposed facilities
CMC Division	Division of Post-Marketing Evaluation, Br. VII
OND division	Division of Anesthesia, Analgesia and Rheumatology Products
Applicant/Sponsor	Ortho-McNeil-Janssen Pharmaceuticals Inc.,
Submission Type	Code NDA 505(b)(1); Priority (CMC Supplement)
Provides for	Transition from Reservoir Patch to Matrix Patch
Formulation	Strength(s) Transdermal Matrix Patch
Proposed Indication	Management of persistent moderate to severe pain

Addendum:

On July 28, 2009 CMC team and the pharmtox team had a teleconference with the applicant. The applicant agreed to the following post-marketing requirement and commitments:

As a post- marketing requirement (1):

- 1) To conduct an in-vivo mouse micronucleus test at the same intravenous doses used for fentanyl (0.63, 2.5 and 10 mg/Kg). The applicant has agreed to submit the final report by March 1, 2010.

As a post-marketing commitments (2-6):

- 2) To reduce the limit of quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of no more than (NMT) (b) (4) ppm. The applicant agreed to submit the final report by January 31, 2010.

- 3) To reduce the limits of detection and quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated. The applicant agreed to submit the final report by January 31, 2010.
- 4) To evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the levels of the material do not exceed 1.5 mcg/day (equivalent to (b) (4) ppm in the product). The applicant agreed to submit the final report by January 31, 2010.
- 5) To evaluate the specificity of the assays used in the leachable/extractable studies. The applicant agreed to submit the final report by January 31, 2010.
- 6) To conduct the Probe Tack test and submit the test method, validation report and specification. The applicant agreed to submit the final report by December 31, 2009.

The drug product was granted 24 month expiry dating period by the reviewer Dr. Amit Mitra.

The above should be noted in the action letter.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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/s/

RAMESH RAGHAVACHARI
07/30/2009
Addendum to the CMC executive summary

JAMES D VIDRA
07/30/2009

ERIC P DUFFY
07/30/2009

Chemistry Review Data Sheet**REVIEW OF CHEMISTRY MANUFACTURING AND
CONTROLS for
DIVISION OF ANESTHESIA, ANALGESIA, AND
RHEUMATOLOGY PRODUCTS****CHEMIST'S REVIEW #1**

1. NDA NUMBER: 19-813
2. NAME AND ADDRESS OF APPLICANT
Johnson & Johnson Pharmaceutical Research & Development, L.L.C
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
3. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED
SCF-044 / 30-JAN-2009 /25-FEB-2009
4. NAME OF THE DRUG: Duragesic (Fentanyl transdermal system)
5. NONPROPRIETARY NAME: Fentanyl Transdermal System
6. SUPPLEMENT PROVIDES FOR: Reformulation
7. AMENDMENTS/REPORTS/ DATE: Amendment/10-APR-2009/28-APR-2009/21-MAY-2009/15-JUL-2009/ 20-JUL-2009/29-JUL-2009
Supporting document/ 28-JUL-2008 (sequence 0012)
8. PHARMACOLOGICAL CATEGORY
Management of persistent, moderate to severe pain
9. HOW DISPENSED
Prescription
10. RELATED IND/NDA/DMF/SUPPLEMENT
None

Executive Summary Section

11. DOSAGE FORM : Transdermal

12. POTENCY

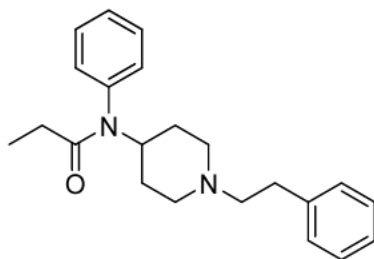
- a. delivering 12 mcg per hour from a patch of surface 5.25 cm^2 containing 2.1 mg fentanyl
- b. delivering 25 mcg per hour from a patch of surface 10.5 cm^2 containing 4.2 mg fentanyl
- c. delivering 50 mcg per hour from a patch of surface 21 cm^2 containing 8.4 mg fentanyl
- d. delivering 75 mcg per hour from a patch of surface 31.5 cm^2 containing 12.6 mg fentanyl
- e. delivering 100 mcg per hour from a patch of surface 42 cm^2 containing 16.8 mg fentanyl

13. CHEMICAL NAME AND STRUCTURE

N-(1-(2-phenylethyl)-4-piperidiny)-N-phenyl-propanamide

Chemical Formula: $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$

MW =336.47



14. COMMENTS

The CMC review is a team review with the agreement from the division director, post approval and the following reviewers as follows.

- Amit Mitra will review Patch construction manufacturing, adhering characteristic and specifications
- Pat Maturu will review DMFs for adhesive components, patch components, and release liner
- John Duan from ONDQA- BioPharm will review release rate

Executive Summary Section

No change in the drug substance is proposed. The applicant has reformulated the drug product. In support of the reformulation the applicant provided the relevant Chemistry, Manufacturing and Controls and Pharmacokinetic data. The adhesive, release liner and backing components, and pouch were reviewed by Dr. Maturu. The release rate was reviewed by Dr. J. Duan. Those reviews are documented separately. The irritation/sensitization, in vivo adhesion and Pharmacokinetic review are being conducted separately.

The drug product is a 3 day patch when applied on the skin for delivery of predetermined amount of fentanyl. At the end of the 3rd day, there will be large amount of residual fentanyl in the patch. Risk assessment for the residual (approximately (b) (4) %) is beyond the scope of CMC review.

The applicant has evaluated the (b) (4) for selection of appropriate acrylate pressure sensitive adhesive.

(b) (4)
Therefore, the acceptance criteria of NMT (b) (4) % is not acceptable since it is above the 1.5 mcg/day threshold for the 100 mcg/hr and 75 mcg/hr strengths.

The residual monomer specification is set by using batch analysis data and toxicity assessment of the residual monomers. Based on the toxicological assessment, the toxicologist has recommended the following revision of the residual monomer acceptance criteria: 1. (b) (4) (NMT (b) (4) ppm), 2. (b) (4) (NMT 1.5 mcg/day exposure). The toxicologist expressed concern for two other potential impurities that could generate from (b) (4). The limit of detection for the leachable assay was not low enough to nullify their presence at unsafe limits. Therefore, the assay method for those compounds should be revised to detect them below their unsafe limits.

The applicant made the following post approval commitments with the agency based on the a T-Con on 28-JUL-2009 and Prior agreement:

- 1) J&J PRD committed to conducting the Probe Tack test and submitting the test method, validation report and specification by the end of this year (31 December 2009).
- 2) J&J PRD will provide data to demonstrate the specificity of the assays used in the leachable/extractable studies. The final report will be provided to the FDA by January 31, 2010.
- 3) J&J PRD commits to evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the

Executive Summary Section

levels of the material do not exceed 1.5 µg/day (equivalent to (b) (4) ppm in the product). The final report will be provided to the FDA by January 31, 2010.

4) J&J PRD commits to attempt to reduce the limits of detection and quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

5) J&J PRD commits to attempt to reduce the limit of quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of NMT (b) (4) ppm. After collection of additional batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

6) Instead of lowering the limit of (b) (4) from NMT (b) (4) % to (b) (4) %, J&J PRD proposes to conduct an in vivo mouse micronucleus test at the same intravenous doses used for fentanyl (0.63, 2.5 and 10 mg/kg).

(b) (4)
Study completion: 1 January 2010
Final Report submission: 1 March 2010

The applicant also provided the LOD for GC-MS method of (b) (4) ppm for the bulk adhesive. The placebo patches produced by J&J and (b) (4) showed no (b) (4) being present. The agreements are satisfactory to the reviewer since the limits for (b) (4) and potentially toxic compounds are satisfactory to the Pharm-Tox reviewer.

Executive Summary Section

This review document was secondary reviewed by Dr. Richard Lostritto, Division Director, Division of Pre-Marketing Assessment III & Manufacturing Science via paper copy review. Since the supplement was submitted in the Post Marketing Division; therefore, the review is being sent for another secondary review to the Post Marketing Division.

15. CONCLUSIONS AND RECOMMENDATIONS:

Post approval commitments are adequate. No deficiency noted.

Reviewed By: Amit K. Mitra, Ph.D.

CC: A. K. MITRA, Ph.D/ONDQA
R.LOSTRITTO, Ph.D/ONDQA
R. RAGHAVACHARI, Ph.D/ONDQA

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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/s/

AMIT K MITRA
07/30/2009

JAMES D VIDRA
07/30/2009

Although this review has already had a secondary review by Dr. Rik Lostrito, I will also provide another secondary review.

ERIC P DUFFY
07/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Swati Patwardhan, RPM, Reviewing Chemist, HFD-01
E-mail Address: swati.patwardhan@fda.hhs.gov
Phone: (301)-796-4085
Fax: (301)-796-9748

FROM: FDA
Division of Pharmaceutical Analysis, HFD-920
James Allgire
Room 1002
1114 Market Street
St. Louis, MO 63101

Through: B. J. Westenberger, Deputy Director, HFD-920
Phone: (314)-539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 19-813/SCF-044

Name of Product: Duragesic (Fentanyl Transdermal System) Patch

Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Applicant's Contact Person: Harindra Abeysinghe, Director, Regulatory Affairs

Address: 1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Telephone: (609) 730-6212 Fax: (609) 730-3091

Date NDA Received by DPA: 03/27/09

Date Samples Received by DPA: 4/30/09

Date Analytical Completed by DPA: 07/06/09

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☒
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

The cover memo and summary of results are attached.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3897

Date: July 6, 2009, 2009
To: Swati Patwardhan Ph.D. (HF-01)
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)
From: Wei Ye, Chemist (HFD-920)
Subject: Method Validation for NDA 19-813
Duragesic (Fentanyl Transdermal System) Patch
Ortho-McNeil-Janssen Pharmaceuticals, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Adhesive Force Test (Peel from Stainless Steel)
(ALZA Analytical Method 5.634 Fentanyl D-TRANS Matrix System, AAM 5.634/XX April 2009/PDF; Section 1-5 Adhesive Force)
2. Release Force Test (Release Liner Removal)
(ALZA Analytical Method 5.634 Fentanyl D-TRANS Matrix System, AAM 5.634/XX April 2009/PDF; Section 1-2, 6-9 Release Force)
3. Drug Release of Fentanyl from D-TRANS Fentanyl Matrix Systems
(ALZA Analytical Method: Drug Release of Fentanyl from D-TRANS Fentanyl Matrix Systems, AAM 1.692, Ver. 3)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods.

1. Adhesive Force Test (Peel from Stainless Steel)
(ALZA Analytical Method 5.634 Fentanyl D-TRANS Matrix System, AAM 5.634/XX April 2009/PDF; Section 1-5 Adhesive Force)
 - Method does not state number of analyses to run per sample.
2. Release Force Test (Release Liner Removal)
(ALZA Analytical Method 5.634 Fentanyl D-TRANS Matrix System, AAM 5.634/XX April 2009/PDF; Section 1-2, 6-9 Release Force)
 - The method does not clearly state whether the (b) (4)
 - Method does not state number of analyses to run per sample.
3. Drug Release of Fentanyl from D-TRANS fentanyl Matrix Systems
(ALZA Analytical Method: Drug Release of Fentanyl from D-TRANS Fentanyl Matrix Systems, AAM 1.692, Ver. 3)
 - (b) (4) speed at a frequency of (b) (4) per minute with amplitude of (b) (4) should be specified in the method.

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this page is the manifestation of the electronic signature.**

/s/

James F Allgire
7/6/2009 06:06:41 PM

Benjamin Westenberger
7/7/2009 11:19:14 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

PHARMACOLOGY REVIEW(S)



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

**SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER:	19-813
SERIAL NUMBER:	S044
DATE RECEIVED BY CENTER:	1/30/2009
PRODUCT:	DURAGESIC (fentanyl transdermal system)
INDICATION:	Persistent, moderate to severe chronic pain
SPONSOR:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	Nonclinical information in the EDR
REVIEW DIVISION:	Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER:	Mamata De, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob A. Rappaport, M.D.
PROJECT MANAGER:	Kathleen Davies

Date of review submission to Division File System (DFS): July 30, 2009

Recommendations

A. Recommendation on approvability

From a nonclinical perspective, this CMC supplement is considered approvable with the following post-marketing commitments to address outstanding concerns regarding several potential and/or (b) (4) drug product impurities. These post-marketing requirements and commitments were discussed with the Sponsor on July 28, 2009. The Sponsor has agreed to these studies as per their email dated July 29, 2009, which is summarized below:

B. Recommendation for nonclinical studies/deficiencies

1. Due to the incomplete genetic toxicology characterization and the prediction of clastogenicity for Impurity B via the FDA Computational Toxicology structure activity analysis, the Sponsor should reduce the drug product specification for fentanyl impurity B to NMT (b) (4) % in order to keep the exposure to NMT 1.5 mcg/day or conduct an in vitro assay to characterize the clastogenic potential of Impurity B that demonstrates a lack of genotoxicity.

J&J Response: J&J committed to conduct an in vivo mouse micronucleus test at the same intravenous doses used for fentanyl (0.63, 2.5, and 10 mg/kg).

Reviewer comment: The proposed in vivo study will be acceptable to address this concern; however, the sponsor should submit a full protocol for review, as the Agency can not commit to the doses proposed without preliminary data. This study will be a post-marketing requirement (PMR).

2. Reduce the levels of (b) (4) in the drug product to less than 1.5 mcg/day (b) (4) ppm) or improve the sensitivity of the analytical technique to clearly demonstrate that the levels of the impurity do not exceed 1.5 mcg/day.

J&J Response: J&J committed to attempt to reduce the levels of detection and quantitation for the analytical method for (b) (4) and to perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

Reviewer comment: The proposed PMC is acceptable. To date, this monomer has not been detected in the drug product patch via the current acceptable methodology. This monomer has been employed in other approved (b) (4), as such, there is unlikely to be any increased risk over and above that posed by the

previously approved transdermal patches employing similar (b) (4). The requested improvements in analytical techniques will result in an improvement in overall drug product quality as the technology advances.

3. Reduce the specification for (b) (4) to NMT (b) (4) ppm. Although the data to date suggest that (b) (4) is a possible human carcinogen, the effect does not appear to be due to direct mutagenicity and therefore a threshold should exist. Based upon the published no-adverse-effect of (b) (4) ppm via inhalation, the proposed specification of NMT (b) (4) ppm should be tightened to NMT (b) (4) ppm.

J&J response: J&J committed to attempt to reduce the limit of quantification for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of NMT (b) (4) ppm. After collection of the additional batch data, the specification will be reevaluated. The final report will be provided to the FDA by January 31, 2010.

Reviewer Comment: This is acceptable. To date, this monomer has not been detected in the drug product patch via the current acceptable methodology.

4. Due to a lack of assay sensitivity, the theoretically exposure to (b) (4) may exceed the threshold for toxicological concern (NMT 1.5 mcg/day) and there are inadequate data regarding the genotoxic potential of this compound. The Sponsor should improve the sensitivity of their assay for this potential impurity to determine if it is present in the patch leachate at levels that would result if exposure that could exceed 1.5 mcg/day, or conduct an in vitro assay to characterize the clastogenic potential of (b) (4) that demonstrates a lack of genotoxicity.

J&J Response: J&J committed to evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the levels of the material do not exceed 1.5 mcg/day (equivalent to (b) (4) ppm in the product). The final report will be provided to the FDA by January 31, 2010.

Reviewer comment: This is acceptable. This is a (b) (4) impurity which has not been detected to date. Should the improved assay methodology demonstrate levels of (b) (4) that exceed the 1.5 mcg/day level, the need for setting a specification and/or further toxicology studies will be reevaluated.

C. Recommendations on labeling

The current FDA approved drug labeling for the Duragesic fentanyl transdermal system was updated to include the result of the carcinogenicity study. All other nonclinical portions of the product labeling remain the same.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
(b) (4)	Carcinogenesis In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in female (b) (4) 0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on AUC _{0-24h} comparison).	Exposure data was included based on information from the 90-day dose-range finding study in the rat compared to the human steady state clinical exposures obtained via clinical study C-2002-047.

Background

The current chemistry supplement (044) was submitted to support a change in drug product manufacturing. Specifically the currently marketed Duragesic transdermal patch is a drug in reservoir design. The chemistry supplement is for a change in the manufacturing of this patch to a drug in matrix design. During a meeting with Sponsor on June 19, 2008, the Division provided the following nonclinical recommendations with respect to the planned CMC supplement submission:

Based on the existing nonclinical and clinical experience with Duragesic drug in reservoir system, the studies described in Table 6 of your submission (single and repeat dose dermal irritation and delayed contact hypersensitivity studies in the guinea pig), in conjunction with the existing clinical experience overseas for the new drug product formulation, may support the safety of the drug product with the following caveats:

- 1. Your sNDA submission should include final study reports for all toxicology studies listed in Table 6, including the qualitative and quantitative composition of the matrix formulations tested in those studies and how the product compares to the proposed clinical formulation.**
- 2. Your sNDA submission must contain information on potential leachables and extractables from the drug product formulation. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short term dosing). Specifically, your NDA supplement should include a toxicological risk assessment for the levels of the residual monomers in the system (b) (4)**

(b) (4) including copies of referenced literature used to support the safety of the residual monomer specifications.

3. We note that (b) (4) does not appear in the Inactive Ingredients Guide, and technically is a novel excipient. Your NDA supplement should provide justification for the safety of this novel excipient. Novel excipients must be adequately qualified for safety. Studies must be submitted to the CMC supplement in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following: <http://www.fda.gov/cder/guidance/guidance.htm>.

a. Please note that “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” (Emphasis added).

4. We note that carcinogenicity studies were initiated for the (b) (4) and are likely completed at this time. Your (b) (4) should include the final study reports from these studies and propose labeling revisions to include the results of these studies.

5. For your sNDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICHQ3A(R) and ICHQ3B(R).

a. Adequate qualification must include:

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

b. Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic residual intermediates in the synthetic scheme unless otherwise justified.

6. Fentanyl drug substance may contain residual intermediates/impurities that contain (b) (4), such as:

(b) (4)

A specification of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic residual intermediates in the synthetic scheme unless otherwise justified.

We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities or provide adequate safety qualification.

- 7. Final determination of the adequacy of safety of the matrix formulation can only be determined after complete review of the toxicology reports submitted with the sNDA.**

Summary of Nonclinical Information Submitted in Support of Supplement 044

Final Study Reports (Dermal toxicity):

The Sponsor submitted final study reports of a primary skin irritation assay, a 28-day repeat-dose skin irritation assay and a dermal hypersensitivity assay. These studies were reviewed by Dr. Mamata De and deemed acceptable. As these studies tested patches containing (b) (4), they adequately characterized the potential local toxicity of the (b) (4) drug product (b) (4). Long-term chronic dermal toxicology studies were not required for (b) (4).

Novel Excipient Extractable Leachable Safety Qualification:

Johnson and Johnson's extractable leachable safety assessment strategy consisted of evaluating the patch extracts for impurities that could be present as a result of being present in the starting materials (either from the fentanyl API, the adhesive, the (b) (4) backing layer or the removable liner. They also examined the extracts for unexpected impurities and based their identification threshold on those described for drug products as per ICHQ3B(R2). The Sponsor employed three different extraction media. Isotonic saline was used to study the leachable materials via a physiological solution. For extractable testing, Johnson and Johnson employed 0.01% formic acid and 100% ethanol. The Sponsor tested samples from both 1-month and 9-month old patches at skin surface temperature of 32°C and body temperature of 37°C. The protocols for these studies were submitted to the Agency during the review cycle and modified as per CMC and Pharmacology Toxicology recommendations provided to the Sponsor on June 16, 2009.

(b) (4) pressure sensitive adhesives have a long history of clinical use in transdermal patches both in the United States and abroad. There are numerous (b) (4) excipients in FDA approved drug products, including (b) (4). However, (b) (4) the particular (b) (4) formulation proposed for use in the reformulated Duragesic drug product, is not use in approved FDA products. According to (b) (4) the manufacturer

The original submission did not contain extractable leachable information on the drug product formulation, and therefore, subsequent discussions with the Sponsor were necessary in order to obtain these data. In a submission received July 2, 2009, the Sponsor provided results of extractable leachable testing with their safety assessment of the findings. Dr. De has concluded that the study designs (solvents, temperatures, duration) are acceptable in terms of the extractable/leachable conditions. The results of the extractable leachables studies are the focus of this memorandum, as the submissions identified numerous compounds that were either confirmed to be in the patch or are potentially in the patch. Each of these will be addressed below.

Drug Substance Specifications:

The drug substance specifications as noted in DMF (b) (4) have not changed and have been previously deemed accepted by the Agency for the original Duragesic drug-in-reservoir formulated product. According to the CMC reviewer of the DMF, Dr. Pramoda Maturu, the (b) (4) impurity specifications are NMT (b) (4) % (the 100 mcg/h patch would deliver (b) (4) mcg/day fentanyl, which would result in exposure to (b) (4) mcg/day of an impurity at this limitation, assuming comparable diffusion). These specifications are acceptable for impurities (b) (4).

Drug Product Specifications:

The highest strength fentanyl patch delivers 100 mcg/hr results in a dose of fentanyl of (b) (4) mg/day. Therefore, the qualification threshold for nongenotoxic drug product degradation products would be NMT (b) (4) or (b) (4) mcg total daily intake, whichever is lower. Although the Sponsor notes that some patients may apply more than one patch at a time, this is considered off-label use of the product.

The Proposed Drug Product Specifications are presented in the Sponsor's table below (reproduced from e-mailed submission dated July 2, 2009):

TABLE 3.2.P.5.1-A: Specifications for D-TRANS[®] fentanyl matrix system 12 µg/h, 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h

Test parameter	Test Methods	Acceptance criteria				
		12 µg/h	25 µg/h	50 µg/h	75 µg/h	100 µg/h
Identification of Fentanyl	AAM 3.337	Sample spectrum exhibits transmittance minima at the same wavelengths as the reference spectrum				

Test parameter	Test Methods	Acceptance criteria				
		12 µg/h	25 µg/h	50 µg/h	75 µg/h	100 µg/h
Appearance	AAM 9.001	(b) (4)				
Fentanyl Assay, Average	AAM 1.691	mg/system	mg/system	mg/system	mg/system	mg/system
		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fentanyl Content Uniformity	AAM 1.691	Conforms to USP <905> Criteria for Transdermal Systems				
Degradation Products, Average	AAM 1.691	(b) (4)				
1. (b) (4)		(b) (4)				
2. (b) (4)	AAM 1.691	(b) (4)				
3. Individual Unspecified	AAM 1.691	(b) (4)				
4. Total Degradation Products	AAM 1.691	(b) (4)				
Drug Release	AAM 1.692	Conforms to USP <724> Acceptance Table 1				
1. 0 - 0.5 h interval		(b) (4)				
2. 0 - 2 h interval		(b) (4)				
3. 0 - 4 h interval		(b) (4)				
4. 0 - 24 h interval		(b) (4)				
Residual (b) (4)	AAM 2.156	(b) (4) ppm				
Adhesive Peel Force- System from Protective Liner, Average	AAM 5.634	(b) (4) g/cm				
Adhesive Peel Force- System from Stainless Steel, Average	AAM 5.634	(b) (4) g/cm				
Residual Monomers (At Lot Release only):	AAM 207554	(b) (4)				
1. (b) (4)		1. NMT	(b) (4)	ppm		
2. (b) (4)		2. NMT	(b) (4)	ppm		
3. (b) (4)		3. NMT	(b) (4)	ppm		
4. Total Residual Monomers		4. NMT	(b) (4)	ppm		
(b) (4) (At Lot Release only):	AAM 207554	NMT (b) (4) ppm				

NOTE: AAM = ALZA Analytical Method; USP = United States Pharmacopeia

Fentanyl related impurities/degradants

The Sponsor included assessments for potential fentanyl related drug substance impurities and/or drug product degradants in the leachable extractable studies. The results are presented in the table below. Values with the < symbol reflect the limit of detection of the assay; indicating that the compound was not detected via the methodology employed.

Table 9. Fentanyl-related Compounds

Compound	Micrograms per patch							
	Isotonic Saline		0.01% Formic Acid			Ethanol		
	1-Month	9-Month	1-Month	9-Month		1-Month	9-Month	
	37°C	37°C	37°C	32°C	37°C	37°C	32°C	37°C
(b) (4)								

(b) (4) respectively.

Of the above impurities, (b) (4) do not contain any structural alerts and are regulated as per general drug substance and drug product impurity specifications. In contrast, (b) (4) contain (b) (4) and should be regulated at the NMT 1.5 mcg/day level. (b) (4) were not detectable even under harsher extraction conditions and, as these potential impurities are several steps (b) (4) in (b) (4) for fentanyl, are unlikely to be present in the drug substance. The limit of detection for (b) (4) would result in a theoretical daily exposure of less than (b) (4) mcg/day, if present at all, from a single 100 mcg/hr patch. Although the limit of detection for (b) (4) precludes the ability to predict that the total daily exposure would be less than (b) (4) mcg/day (b) (4) days (b) (4) mcg/day), this compound is regulated at the level of the drug substance and is not believed to be a drug product degradant. Of the five potential (b) (4) fentanyl related impurities, only Impurity (b) (4) appears to also be a drug product (b) (4) and therefore a drug product specification was established.

(b) (4)

(b) (4)

(b) (4) The proposed specification for the (b) (4) is NMT (b) (4) ppm. (b) (4) is a (b) (4) as per ICH Q3C. As per ICH Q3C, a specification of up to (u) (4) ppm or (u) (4) % would be acceptable without justification. Therefore, the proposed specification is acceptable.

***Reviewer Recommendation:** No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity at the specified level.*

Residual Monomers. The Sponsor was asked to include specifications for the residual monomers, (b) (4). The proposed product release specifications and the amounts found following a batch analysis are presented in the table below reproduced from the Sponsor's submission:

(b) (4)

Each of these will be addressed separately below:

(b) (4) To date, (b) (4) has not been detected as a leachable/extractable in the solvents employed. The proposed specification for (b) (4) is NMT (b) (4) ppm. A specification of NMT (b) (4) ppm would result in (b) (4) mcg/patch or (b) (4) mcg/day. In the extractable leachable studies, the reported level of quantitation for this potential (b) (4) is (b) (4) ppm. However, this residual monomer was not detected in the extractable leachable study with a reported level of detection of (b) (4) ppm ((b) (4) mcg per patch). The available toxicity data from the published literature report both positive and negative genetic toxicology data (b) (4). There is a single referenced report that examined the potential carcinogenicity of (b) (4) in rats following 18 months inhalation. Although there was no evidence for tumor formation reported, the highest dose tested was only (b) (4) ppm (reference to (b) (4) report not available). Therefore, there are no carcinogenicity data that have evaluated adequate exposures to allow extrapolation of safety at the proposed level of (b) (4) ppm. I agree with Dr. De that the carcinogenic potential of this compound at the potential levels in the patch (assuming 100% absorption) has not been adequately evaluated; therefore, given the positive genetic toxicology findings to date, the levels of this drug product formulation impurity should be reduced to NMT 1.5 mcg/day (b) (4) ppm). The sensitivity of the analytical technique employed by the Sponsor to date precludes the ability to determine if there is less than (b) (4) mcg/day exposure to this impurity.

Reviewer Recommendation: Due to the positive results in some genetic toxicology studies and the lack of adequate carcinogenicity assessment for (b) (4) the Sponsor should reduce the levels of (b) (4) in the drug product to less than 1.5 mcg/day (b) (4) ppm) or improve the sensitivity of the analytical technique to clearly demonstrate that the leachable levels of the impurity will not result in exposure that would exceed 1.5 mcg/day. According to the CMC review team, the analytical methodology employed by the Sponsor to measure (b) (4) in the extraction media is adequate and acceptable based on current standards. Therefore, as (b) (4) was not detected in any of the extraction media, the Sponsor has provided adequate data to indicate that this potential residual monomer is not present in the drug product with adequate sensitivity to allow approval of the product. Nonetheless, as the potential levels at the proposed specification with exceed the threshold of toxicological concern, the Sponsor should commit to improving their analytical technique as a post marketing commitment. As per the email dated July 29, 2009, the Sponsor has committed to attempt to reduce the limits of detection and quantitation for (b) (4) and reevaluate the specification by January 31, 2010.

(b) (4) The proposed specification for (b) (4) is NMT (b) (4) ppm. In the extractable leachable studies, the level of quantitation for this potential residual solvent is (b) (4) ppm. However, this residual monomer was detected in the extractable leachable study a (b) (4) ppm. A specification of NMT (b) (4) ppm would result in (b) (4) mcg/patch or (b) (4) mcg/day. The available toxicity data from the published literature report suggest that (b) (4) tests negative in the in vitro Ames assay and the in vitro chromosome aberrations assays; however, (b) (4)

(b) (4) Dr. De notes that there are two published studies that demonstrate a positive carcinogenic effect (neoplastic skin lesions including papillomas,

carcinomas and melanomas) at high doses of (b) (4)

Both of these studies reported a NOAEL for dermal carcinogenicity. In contrast to these two earlier studies, a 2-year carcinogenicity study in male NMRI mice with (b) (4)

Although the data from these studies is not available for peer review, the weight of evidence suggests that although potentially clastogenic and carcinogenic at higher doses, three studies have reported a NOAEL for dermal carcinogenicity, suggesting minimal toxicological concern for the Duragesic product. Although the studies would not likely meet current standards, the proposed specification of NMT (b) (4) ppm does not raise safety concerns.

***Reviewer Recommendation:** No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity at the specified level.*

(b) (4) The proposed specification for (b) (4) is NMT (b) (4) ppm. A specification of NMT (b) (4) ppm would result in (b) (4) mcg/patch or (b) (4) mcg/day. The available toxicity data from the published literature report that (b) (4) tests negative in the Ames assay (b) (4) however, (b) (4) is a confirmed animal carcinogen with unknown relevance to humans (b) (4)

Collectively, these data suggest that the carcinogenic effects of (b) (4) likely have a threshold and therefore should demonstrate a NOAEL level. IARC concludes that (b) (4) is possibly carcinogenic to humans. The US EPA sets a NOAEL for nasal carcinogenicity via inhalation at (b) (4) ppm. A LOAEL of (b) (4) ppm was reported due to the presence of nasal basal cell hyperplasia at this exposure level. In the extractable leachable studies, the level of quantitation for this potential (b) (4) is (b) (4) ppm. However, this residual monomer was not detected in the extractable leachable study with a level of detection of (b) (4) ppm ((b) (4) mcg per patch). The proposed specification is between the NOAEL and the LOAEL for nasal epithelial cell hyperplastic changes. (b) (4)

As the carcinogenic effects of (b) (4) to be located at the site of contact, and the Duragesic patch is moved from site to site, the potential risk due to local tissue contact is less than that which produced hyperplasia in the nasal epithelium. However as (b) (4) was not detected in the extractable leachable study, and the level of detection is (b) (4) ppm, the specification should be tightened to NMT (b) (4) ppm or as low as technically feasible.

***Reviewer Recommendation:** Further action required. Although the data to date suggest that (b) (4) is a possible human carcinogen, the effect does not appear to be due to direct mutagenicity and therefore a threshold should exist. Based upon the published no-adverse-effect level of (b) (4) ppm via inhalation, the proposed specification of NMT (b) (4) ppm should be tightened to NMT (b) (4) ppm. This was discussed with the Sponsor on July 28, 2009. As per the email dated July 29, 2009, the Sponsor committed to improving the analytical capability to reduce the specification to NMT (b) (4) ppm.*

(b) (4) is the (b) (4) which undergoes (b) (4). The Sponsor does not set a specification for this potential drug product impurity, as the (b) (4). According to the Sponsor, (b) (4) does not contain any (b) (4) as per the (b) (4) software program. A search of the available toxicology databases also suggests that (b) (4) is not genotoxic. Based on these data, residual (b) (4) could be regulated as a nongenotoxic drug product impurity. According to the Sponsor, (b) (4) ppm and it was not detected in extracts of the placebo matrix patches in studies conducted by (b) (4). Given the lack of evidence for genotoxic potential, the low levels in the (b) (4), and the likelihood that the (b) (4) there is no clear need to set a specification for this potential drug product impurity.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity at the specified level. As this impurity would appear (b) (4) and has not been detected in the leachable extractable solutions, a specification is not necessary.

(b) (4) a (b) (4) of the (b) (4) is described as nonmutagenic via a (b) (4) analysis. Evaluation of batch records suggest that (b) (4) ppm (b) (4) has been detected in patches. The Sponsor has proposed a specification of NMT (b) (4) ppm. (b) (4) has also been reported to be negative in the Ames assay (b) (4). Based on existing genetic toxicology information, (b) (4) should be treated as a nonmutagenic impurity. However, (b) (4) is a known neurotoxic compound and OSHA sets a permissible exposure limit (PEL) and NIOSH set a recommended exposure limit (REL) for (b) (4) for skin at (b) (4) ppm. The toxicity of (b) (4) was characterized primarily via 90-day repeat dose oral gavage toxicology studies in the rat and dog models (b) (4); however, the actual study report was not supplied by the Sponsor nor available at the time of this memorandum. A summary of the results of these studies was obtained by Dr. De via a report completed by the Health Council of the Netherlands completed to determine a health-based occupational exposure limit. Based on this summary alone, the NOAEL of (b) (4) mg/kg via oral gavage was reported with the primary toxicity defining the NOAEL being renal tubular nephrosis. The committee reviewing the data did not feel that the kidney findings in the rat were clinically relevant and based their risk assessment on a NOAEL of (b) (4) mg/kg/day due to liver findings in the rat model. This dose is equivalent to (b) (4) mg/m² based on body surface area. A patch containing (b) (4) ppm (b) (4) would contain (b) (4) mcg/patch ((b) (4) mcg/day = (b) (4) mg/m²). Therefore, the rat 90-day NOAEL of (b) (4) mg/kg provides an exposure margin of (b) (4) for the predicted human exposure to a single patch. Given the existing human experience with other (b) (4) that have employed the same (b) (4) and therefore also contain (b) (4) the apparent safety margin based on the 90-day repeat dose toxicology study that has been the basis for occupational exposure assessments in the US and abroad, the proposed specification of NMT (b) (4) ppm for (b) (4) does not appear to represent a clinically significant safety concern and this therefore acceptable.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity at the specified level.

Other nonspecified (b) (4) extractables and leachables:

(b) (4) In their extraction studies, Johnson & Johnson detected the compound (b) (4) at levels of up to (b) (4) mcg/patch (ethanol, 37°C); however, the level was (b) (4) mcg/patch when saline was used as the solvent. A specification has not been proposed. The existing data in the published literature suggests that (b) (4) is negative in the Ames assay (b) (4) and does not result in tumor formation in the rat or mouse model (b) (4). The low doses in the carcinogenicity study appear to be the NOAEL/LOAEL for general toxicity (b) (4) mg/kg). This dose is approximately (b) (4)-fold higher than the daily human exposure to a patch containing (b) (4) mcg of (b) (4) based on a body surface area comparison. As such, there does not appear to be any safety concerns with this potential drug product impurity.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification does not appear warranted based on the existing toxicology data.

(b) (4) was also detected in the 32°C 9-month formic acid extract at a level of (b) (4) mcg/patch ((b) (4) mcg/day = (b) (4) mg/m²); however, this was not detected in the saline extracts. A specification has not been proposed. The existing published information suggest that (b) (4) tested negative for mutagenicity in the standards strains employed for the Ames assay (b) (4) and the CHO cell assay (b) (4) however, there are a few positive findings reported for the mouse lymphoma assay (b) (4). The NTP has conducted both rat and mouse carcinogenicity studies that concluded that there was no evidence for carcinogenicity in the rat and some evidence for carcinogenicity in the mouse (forestomach) (National Toxicology Program, 1990). Given the genetic toxicology data, any carcinogenic effect is likely to have a threshold. Further, in terms of general toxicity, the IRIS database lists a NOAEL level for forestomach lesions and kidney toxicity of (b) (4) mg/kg/day ((b) (4) mg/m²). Based on body surface area, this would provide an exposure margin of (b) (4)-fold the worst-case human exposure from a single patch. Collectively, the theoretical exposure to (b) (4) mcg/patch does not suggest a safety concern.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification is not necessary.

In addition, the Sponsor identified several (b) (4) impurities in the drug product, including other potential (b) (4) breakdown products: (b) (4)

(b) (4) In addition, the patch could theoretically contain trace levels of free radical scavengers: (b) (4)

(b) (4) The table below, reproduced from the extractable leachable report from Johnson & Johnson indicates that none of the potential identified extractables were detected at either temperature in any of the solvents tested. However, it should be noted

that the limit of detection differed for these potential extractables and several of these could not be detected due to the lack of reference standards or analytical methodology challenges.

Table 10. Potential Extractables

Compound	Micrograms per patch							
	Isotonic Saline		0.01% Formic Acid			Ethanol		
	1-Month	9-Month	1-Month	9-Month		1-Month	9-Month	
	37°C	37°C	37°C	32°C	37°C	37°C	32°C	37°C
(b) (4)								

ND = None detected by GC-MS

NQ = Not quantifiable and/or detectable by methodology employed.

TR = Trace levels of (b) (4) were detected in two samples

* = No reference standard was available for these compounds, however, the parent ions were not detected by GC-MS.

In addition to the studies conducted by Johnson and Johnson, (b) (4) also conducted extraction studies of placebo patches using harsher solvents (ethyl acetate and tetrahydrofuran). The table below outlines the results of the (b) (4) studies that looked for these (b) (4) impurities.

Placebo Patches Extraction Data from (b) (4)	
Analyte	Concentration (ppm)
(b) (4)	

Concentrations were determined following extraction of intact patches with ethyl acetate or tetrahydrofuran.

As noted in the table above, none of the above (b) (4) contaminants were detected with the typical limit of detection of (b) (4) ppm. The level of (b) (4) ppm would result in a maximum daily

exposure to (b) (4) mcg/patch (b) (4) mcg/day, assuming 100% absorption from the patch) for (b) (4) solid components of the adhesive. As the estimate of (b) (4) mcg/day represents an extreme condition under nonphysiological conditions and assumes 100% absorption, the actual exposure is probably lower. Since the threshold for toxicological concern for genotoxic impurities is NMT 1.5 mcg/day, and the limit of detection reported by (b) (4) represents a worst case scenario for (b) (4) impurities in the drug product assuming 100% absorption from the patch, the weight-of-evidence does not suggest significant toxicological concern. Nonetheless, each of these will be addressed individually below taking into consideration the limits of detection from both the Johnson and Johnson and (b) (4) results.

(b) (4) was identified as a likely minor byproduct of (b) (4) breakdown (primary breakdown product is (b) (4) was not detected by Johnson and Johnson in any of the extractable solutions with a limit of detection of (b) (4) mcg/patch. (b) (4) could also not detect this potential impurity with a limit of detection of (b) (4) in the placebo patches nor in the bulk (b) (4) solutions with a limit of detection of (b) (4) ppm. A search of the published literature suggests that (b) (4) has been reported negative in the Ames assay (b) (4) the in vivo micronucleus assay, and negative in both the rat and mouse carcinogenicity studies (National Toxicology Program, 2001). Assuming up to (b) (4) ppm in a patch, the patch would contain NMT (b) (4) mcg (b) (4) mcg/day), which is below the threshold for toxicological concern.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification is not necessary.

(b) (4) (also known as (b) (4) was identified as a second likely minor byproduct of (b) (4) breakdown (primary breakdown product is (b) (4) was not able to be quantified by Johnson and Johnson in any of the extractable solutions. (b) (4) could also not detect this potential impurity with a limit of detection of (b) (4) ppm in the placebo patches; however, they were able to detect a mean of (b) (4) ppm in the bulk (b) (4) solution lots (mean of (b) (4) lots tested, highest lot contained (b) (4) ppm). If (b) (4) is present at (b) (4) ppm in the patch, there would be (b) (4) mcg/patch ((b) (4) mcg/day assuming 100% absorption). There are limited data on the potential toxicity of (b) (4); however, it is known to form (b) (4). According to HSDB (references Patty's Industrial Hygiene and Toxicology), rats exposed to (b) (4) ppm via inhalation for one hour had convulsion and died (cause of death likely due to (b) (4) formation). It has been reported to cause liver injury in rat feeding studies (see HSDB reference to Ethyl Browning's Toxicity and Metabolism of Industrial Solvents). The National Toxicology Program reports negative findings for mutagenicity in the Ames Assay. Although the clastogenic potential of (b) (4) has not been determined, if the compound were clastogenic, concerns regarding carcinogenicity would likely have a threshold and NOAEL could be identified. NIOSH has established an occupation REL (reasonable exposure limit) of (b) (4) ppm via inhalation. A specification of NMT (b) (4) ppm would limit exposure to (b) (4) mcg/day ((b) (4) mcg/patch); which would be below the threshold for toxicological concern for a genotoxic compound. The sensitivity of the assay methodology was discussed with the Sponsor during a teleconference held July 28, 2009. As per the email dated July 29, 2009, the Sponsor indicated that the sensitivity of the GC-MS analysis was also (b) (4) ppm. Although

this could theoretically result in (b) (4) mcg/day, any (b) (4) formed would result from (b) (4). As (b) (4) was not detected at levels of (b) (4) ppm and most of the (b) (4) would be converted to (b) (4) the levels of (b) (4) if present are likely around the (b) (4) ppm levels set by NIOSH. Given the high volatility of this chemical, the sensitivity of the assays employed to date, and the theoretical presence only, there do not appear to be any safety concerns due to the potential presence of (b) (4). No further studies are required.

Reviewer Recommendation: No further action required. The Sponsor has looked for this chemical and can not detect it in any of the extraction solutions via GC-MS. As noted by the CMC review team, the analytical methodology employed by the Sponsor is adequate and acceptable based on current standards.

(b) (4) According to the study report submitted by Johnson & Johnson, (b) (4) is not quantifiable or detectable. (b) (4) is a known impurity in both the (b) (4) (u) (4) (u) (4) sets a specification of NMT (b) (4) % by weight for (b) (4) in the bulk (b) (4) mixture. Given the low boiling point of (b) (4) °C, any (b) (4) impurity would likely be removed in the (b) (4) process. It was not detected in the (b) (4) solution with a level of detection of (u) (4) ppm, nor in the placebo patches with a level of detection of (b) (4) ppm (b) (4). At (b) (4) ppm, a patch would contain (b) (4) mcg which would lead to (b) (4) mcg/day for a 60 kg person. This level is below the threshold of toxicological concern of 1.5 mcg/day; therefore there are no toxicological concerns regarding the potential presence of (b) (4) in this product.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification is not necessary.

(b) (4) was not detected in one patch of (b) (4) lot examined by (b) (4) with an assay sensitivity of (b) (4) ppb. The level of detection reported by Johnson & Johnson is (b) (4) mcg/patch (b) (4) mcg/day). (b) (4)

(b) (4) In two year carcinogenicity studies conducted by the NTP, there was some evidence of carcinogenic activity in rats and mice (National Toxicology Program, 1989). However it is also a component of and FDA-approved combination topical drug product (b) (4) (u) (4) (u) (4). In 2-year oral gavage studies conducted by the NTP, (u) (4) mg/kg (b) (4) was designated the LOAEL in the rat (defined by kidney effects). This dose is (b) (4) -fold greater than the human daily dose of (b) (4) mcg/day from a single patch based on body surface area comparisons. As the (b) (4), if present in the patch, would be derived from the (b) (4) lot, and the level of detection in the assay completed by (b) (4) is far greater than that used by Johnson & Johnson, the (b) (4) -fold exposure margin is likely an under estimate. Therefore, there does not appear to be any safety concern based on the (b) (4) potential that (b) (4) may be in the patch.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification is not necessary.

(b) (4) is employed as a (b) (4) that is present as a (b) (4) in both the (b) (4) monomer (NMT (b) (4) ppm) used in the production of (b) (4). According to the Sponsor, the (b) (4) will be consumed in the (b) (4). (b) (4) levels are controlled in the (b) (4) specifications by (b) (4) and levels are described as below the limit of detection in the (b) (4) solution. Johnson and Johnson does not detect (b) (4) in any of the extraction solutions (level of detection < (b) (4) mcg/patch). If present at (b) (4) mcg/patch, assuming 100% absorption over the course of patch application would result in (b) (4) mcg/day (b) (4) mg/m² for a 60 kg person). Data in the toxicity of (b) (4) suggest that this compound tests negative in the Ames assay for mutagenicity (b) (4). (b) (4) however, due to the design of that study, a NOAEL level for carcinoma can not be determined. In a second study conducted only in male rats, dietary administration of (b) (4) did not result in such tumors, suggesting a threshold for toxicity (b) (4) however, this study did not report amounts of (b) (4) ingested by the animals, therefore, it is not possible to directly establish a safety margin from this study. However, a crude estimate of (b) (4) exposures in this study of approximately (b) (4) mg/kg ((b) (4) mg/m²). Based on a body surface area comparison, this would roughly translate into a (b) (4) -fold safety margin for carcinogenicity for the (b) (4) mcg/day maximum dose of (b) (4) via this product. As such, there does not appear to be any concern related to levels of (b) (4) in this product.

Reviewer Recommendation: No further action required. The weight-of-evidence does not suggest a safety concern for this potential impurity and a specification is not necessary.

(b) (4) is an impurity in the bulk (b) (4) monomer (up to (b) (4) %) used in the production of (b) (4). According to the Sponsor this will be (b) (4) in the formation of (b) (4). Johnson & Johnson did not detect (b) (4) in any of the extraction solutions above the level of detection of (b) (4) mcg/patch ((b) (4) mcg/day). (b) (4) analysis of the placebo patches did not detect (b) (4) above their detection level of (b) (4) ppm ((b) (4) mcg/patch or (b) (4) mcg/day). Therefore, it is possible that the patch could deliver (b) (4) mcg/day of this compound. Information in the published literature suggest that (b) (4). Therefore, a NOAEL for carcinogenicity likely exists; however, no carcinogenicity data exists to establish a NOAEL. No repeat-dose toxicology data were identified in the published literature. The theoretical daily dose of (b) (4) mcg/day would exceed the threshold for toxicological concern for a genotoxic compound of NMT 1.5 mcg/day.

Reviewer Recommendation: Due to a lack of assay sensitivity, the theoretically exposure to (b) (4) may exceed the threshold for toxicological concern (NMT 1.5 mcg/day) and there are inadequate data regarding the genotoxic potential of this compound. The Sponsor should improve the sensitivity of their assay for this likely potential impurity to determine if it is present in the patch leachate at levels that would result if exposure that could exceed 1.5 mcg/day, or conduct an in vitro assay to characterize the clastogenic potential of (b) (4) that demonstrates a lack of genotoxicity. As noted by the CMC review team, the analytical methodology employed by the Sponsor is adequate and acceptable based on current standards. Therefore, the Sponsor should commit to development of a better assay for this impurity as a PMC.

(b) (4) is described as a (b) (4) of (b) (4) breakdown; however, this chemical was not detectable in the extraction solutions via GC-MS (there was no reference standard available; therefore the GC-MS analysis was based on the MW of the compound).

Reviewer Recommendation: No further action required. The Sponsor has looked for this chemical and can not detect it in any of the extraction solutions via GC-MS. Therefore, a specification is not necessary. As noted by the CMC review team, the analytical methodology employed by the Sponsor is adequate and acceptable based on current standards.

(b) (4) described as a (b) (4) byproduct of (b) (4) degradation; however, this chemical was not detectable in the extraction solutions via GC-MS (there was no reference standard available; therefore the GC-MS analysis was based on the MW of the compound). There are limited data on this chemical in the published literature; however, the Sponsor notes that a (b) (4) analysis does not predict genotoxicity.

Reviewer Recommendation: No further action required. The Sponsor has looked for this chemical and can not detect it in any of the extraction solutions via GC-MS. Therefore, a specification is not necessary. As noted by the CMC review team, the analytical methodology employed by the Sponsor is adequate and acceptable based on current standards.

(b) (4) was not detectable in the extraction solutions via GC-MS (there was no reference standard available; therefore the GC-MS analysis was based on the MW of the compound).

Reviewer Recommendation: No further action required. The Sponsor has looked for this chemical and can not detect it in any of the extraction solutions via GC-MS. Therefore, a specification is not necessary. As noted by the CMC review team, the analytical methodology employed by the Sponsor is adequate and acceptable based on current standards.

Carcinogenicity:

As discussed during the meeting with the Sponsor in July of 2008, the Sponsor submitted the final study report for a 2-year rat bioassay. This study report was reviewed by Drs. Leshin and Wasserman the results were discussed by the Executive Carcinogenicity Assessment Committee (ExecCAC). Both the Division and the ExecCAC concluded that the study was deemed valid and the results were negative. The Sponsor's proposed labeling does not include any relative exposure information; therefore, the human to animal ratios will be based on a pharmacokinetic exposure data (AUC only) following a 100 mcg/hr patch. The labeling proposed via the Sponsor's email submission dated July 29, 2009 (attached to this review) proposes to employ both AUC (b)(4) comparisons. However, as the rodent plasma (b)(4) and the human data is (b)(4), comparison of these data is inappropriate. Only the AUC_{0-24h} exposure data will be employed for the labeling.

Of note, the carcinogenicity study did report regions of necrotic tissue in the brains of the rats chronically treated with fentanyl. Given the long clinical use of fentanyl transdermal products, the clinical significance of this finding is unclear. The Sponsor speculates that the effects may have resulted from ischemia due to the known respiratory depressant effects of fentanyl. However, as the carcinogenicity study was conducted via injection rather than transdermal application, which would produce different pharmacokinetic exposures, it is possible that the effect may be related to the route of administration. Careful review of that particular finding will be required in order to determine, what, if anything, should be done to further characterize this finding.

Nonclinical safety issues relevant to clinical use

The proposed drug-in-matrix reformulation of the Duragesic patch includes a novel excipient, (b)(4). In terms of general toxicity, the safety of this novel (b)(4) excipient was established via the nonclinical dermal toxicology studies and the existing clinical experience with (b)(4). The monomers and other chemicals used in the formation of (b)(4) materials are highly reactive compounds that typically show significant toxicity, potentially including genotoxicity and carcinogenicity. Genotoxicity and carcinogenicity can not be assessed via the existing clinical experience or general toxicity studies. As such, justification of their safety must be based on evaluation of the potential extractable and leachable materials from the (b)(4) formulation and adequate data upon which to base a justifiable toxicological risk assessment.

The Sponsor has conducted extractable leachable testing and has proposed to set specifications for the residual monomers as well as one other impurity, (b)(4). However, the Sponsor has not provided adequate information regarding actual levels of several potential extractables and leachables from the drug product formulation and the proposed specifications for some would result in levels that could exceed the threshold for toxicological concern. Nonetheless, as noted by the CMC review team, the analytical methodology employed by the

Sponsor is adequate and acceptable based on current standards. Therefore, the Sponsor has appropriately looked for and failed to detect several potential impurities that may (b) (4) be present in the drug product. However, (b) (4)

the Sponsor should commit to improving the analytical sensitivity of their assay to provide more definitive information regarding the potential levels of these impurities in the drug product as a PMC.

The potential clinical significance of the proposed levels of the drug product impurities is based on reported positive findings in genetic toxicology studies and/or published carcinogenicity studies in rodents. The levels of each of these impurities as assessed via a worst case scenario will exceed the threshold of toxicological concern for increasing the likelihood to develop tumors, most likely at the site of application. As noted in the December 2008 published Draft FDA "Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches", limiting a genotoxic impurity to NMT 1.5 mcg/day is thought to not pose a significant risk for carcinogenicity. The threshold corresponds to a 10^{-5} (1 in 100,000) lifetime risk of cancer. Exceeding the 1.5 mcg/day level is thought to incrementally increase the lifetime risk of cancer. However, as the sponsor has not detected these (b) (4) impurities via adequate analytical methods to date, there are no data to suggest that the drug product would result in any increased risk of cancer due to potential leachables/extractables.

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page.

Attachment (emailed submission from Sponsor dated July 29, 2009 reproduced verbatim):

Justification for Exposure Ratios for Carcinogenicity Labelling for Duragesic

The carcinogenic potential of fentanyl (active ingredient in Duragesic) was evaluated by subcutaneous injection in rats. The maximum tolerated dose in male rats was 33 µg/kg/day for 97 weeks, and 100 µg/kg/day in female rats for 102 weeks. Toxicokinetics were not taken in conjunction with the carcinogenic study, but were determined at these same dose levels in conjunction with a three-month dose range finding (DRF) study in the same species/strain of animals.

Carcinogenicity Exposure Parameter (Day 90, DRF)	Male	Female
Dose (MTD, µg/kg/day)	33	100
C _{max} (ng/ml)	12.72	19.03
AUC _{0-24 h} (ng.h/ml)	12.19	30.04

Data from Study TR-01-5715-024

Following repeated application of the Duragesic patch, steady state is achieved by 72 h after application of the second patch. The daily exposure of fentanyl at steady-state (AUC_{0-24 h}) has been determined from C-2002-047.

Clinical Exposure Parameter (steady state)	M & F, combined
Dose	100 µg/h
C _{ss} (ng/ml)	4.20
AUC _{ss, 0-24} (ng.h/ml)	75.8

Data from study C-2002-047

The daily exposure multiples were determined from male and female rats by comparing the C_{max} and AUC_{0-24 h} from the DRF study and the daily steady-state exposure parameters from the clinical study.

Ratio – Exposure Parameter	Male rats	Female rats
C _{max/ ss}	(b) (4)	
AUC _{0-24 h}	0.16	0.39

Therefore the labelling change in the carcinogenicity section is changed from a comparison of (b) (4) equivalents to the (b) (4):

From:

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100

µg/kg/day in females

(b) (4)

To:

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females.

(b) (4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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

/s/

RICHARD D MELLON
07/30/2009



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	sNDA 19-813
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	01/30/2009
PRODUCT:	Duragesic (Fentanyl transdermal ® system) CII
INTENDED CLINICAL POPULATION:	Patients requiring around the clock relief of persistent moderate to severe pain for an extended period of time
APPLICANT:	Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
DOCUMENTS REVIEWED:	eCTD Module 2 and 4
REVIEW DIVISION:	Division of Anesthesia, Analgesia, and Rheumatology Products (HFD- 170)
PHARM/TOX REVIEWER:	Mamata De, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob A. Rappaport, M.D.
PROJECT MANAGER:	Katherine Davis

Date of review submission to DARRTS: July 29, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the pharmacology toxicology perspective, sNDA 19-813(fentanyl transdermal delivery system) should be considered approvable, upon adequate qualification of the extractables and leachables.

B. Recommendation for nonclinical studies

1. The fentanyl related genotoxic impurities should limit to 1.5 mcg/day or qualified in the mutagenicity assays.
2. Adequate safety evaluation of potential genotoxic impurities such as (b) (4) should be submitted. Alternatively the level of such impurities should be reduced to <1.5 mcg/day, if detected during manufacturing of the finished product.
3. The specifications of the (b) (4) such as (b) (4) should be reduced as per manufacturing capabilities because toxicity evaluation of these (b) (4) are not adequate to predict their carcinogenicity potential. Since (b) (4) is mutagenic, the specification of this monomer needs to be reduced to <1.5 mcg/day, if detected during the manufacturing process.

C. Recommendations on labeling

There were no new genotoxicity and reproductive toxicity data submitted with this NDA, therefore, Applicant's label mimicking current Duragesic label is appropriate for the sNDA19813.

The Applicant, however, submitted carcinogenicity data from rat bioassay which was reviewed by Dr. L.S. Leshin. The review is appended (Appendix 1) with the current review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Duragesic® (Fentanyl Transdermal Matrix system) is a drug-in-adhesive transdermal patch in which fentanyl base is incorporated into a (b) (4) layer of pressure sensitive acrylate adhesive (b) (4). The matrix system eliminates possibility of fentanyl gel leakage and is considered as an improvement over the currently used Duragesic reservoir patch product. Fentanyl is a mu-opioid receptor agonist; the analgesic property of fentanyl has been utilized in a wide variety of marketed product for anesthetics and pain management.

The current product, fentanyl in matrix is designed for pain management with dose and duration similar to the marketed product; however, the (b) (4) contains a novel excipient, (b) (4). Therefore the safety evaluation of the current product is focused mainly on the qualification of the excipient. In addition, the Applicant submitted carcinogenicity data with fentanyl base from rat 108-week bioassay.

To demonstrate the safety of the drug in adhesive matrix formulation, the Applicant submitted acute and subchronic irritation studies in guinea-pigs. It is observed that with an average skin flux of 1.15-1.35 mcg/cm².hr for 96 hr in the hairless guinea-pigs, the primary irritation is negligible. The skin histology assessment revealed increase inflammation in the dermis in all animals applied topically with the transdermal patch compared to that of the naïve skin. One of the animals in which the transdermal patch w/fentanyl treated skin showed PII also showed inflammation of the panniculus (adipose tissue). This finding was characterized by infiltration of macrophages, lymphocytes, and neutrophils in the panniculus.

The cumulative irritation index was assessed in guinea-pigs for 21 days, the fentanyl transdermal system was observed to be mild irritant this study with a skin flux of 2.5-3.47 mcg/cm².hr. The histopathology findings in the subchronic study showed that parakeratosis were noted in 3/5 females in applied with transdermal patch containing fentanyl. The findings suggest that the parakeratosis might be a drug induced effect. Also, there was no sensitization in guinea-pigs with a fentanyl efflux up to 3.17 mcg/cm².hr.

The Applicant referred to the non clinical safety evaluation conducted by (b) (4) for the evaluation of the safety of the novel excipient (b) (4) which was submitted with the DMF (b) (4). The toxicity studies conducted with (b) (4) were based on the classification of the transdermal device as an external device on intact skin for short term duration. The cytotoxicity evaluation was conducted for the biocompatibility assessment after the elution of the (b) (4) in the cell culture solution according to USP; no cytotoxicity observed in this assay. The extracts of the test articles were also used for the evaluation of the acute systemic toxicity in mice (5 male mouse single injections via IV or IP), intracutaneous (IC) toxicity study in rabbit (2 rabbits, single IC injection), and implantation toxicity in rabbit (2 rabbits implanted intramuscularly with the (b) (4)). None of these above mentioned studies showed any toxicity. Note that with the limited number of animals and duration of the dosage application, the study protocol although met USP standard are not ideal for the chronic use of the product. The residual monomers present in the (b) (4). Toxicity studies available in literature were submitted to support the safety evaluation of these monomers.

B. Nonclinical safety issues relevant to clinical use

The Duragesic® fentanyl transdermal system is intended to be used chronically. The cumulative irritation index showed mild irritation in guinea pigs topically administered with the fentanyl transdermal patch. The transdermal delivery system containing the (b) (4) might have irritation potential. This is observed in non clinical studies with vehicle control patches and expected to be reflected in clinical situation. The transdermal fentanyl system w/fentanyl showed parakeratosis and inflammation in guinea pigs. Although the skin efflux ($2.5 \text{ mcg/cm}^2 \cdot \text{hr}$) in non clinical settings are approximately 5-fold higher than that of the expected skin efflux in human ($0.48 \text{ mcg/cm}^2 \cdot \text{hr}$), possibilities of similar skin lesions in human with chronic duration of the patch application could not be dismissed.

(b)
)
(4
)

The Applicant conducted an extractable/leachable study for the finished patch minus the backing layer. The results from this study showed that there were potential impurities which were identified, and quantified, and also which are identified and not quantified. The methods used to quantify the potential

(b) (4)

One group of leachates named

(b) (4)

were identified. The assay methods for these impurities could only quantify the above mentioned chemicals to their lower limit of detections. The toxicity information of these chemicals was not appropriately synthesized by the Applicant. The publicly available literature evaluated by the reviewer, showed (b) (4) has been used in different skin ointments as antioxidant and may pose little concern for toxicity; however, (b) (4) need to be evaluated for toxicity. The Applicant should summarize the toxicity information and establish specification for these compounds if necessary.

Another group of potential leachates such as

(b) (4)

not be detected using the methods employed in the current study. Given the fact some of these chemicals might be carcinogen and neurotoxin, the Applicant have to explore methods to detect/quantify for these potential to reassure that these impurities are present only below the toxicological threshold.

A third group of potential chemicals such as (b) (4) were not quantitated because the reference material were not commercially available. The Applicant mentioned that the (b) (4) method showed that if present, the amount of these impurities might be very low. The Applicant should appropriately justify the safety of these potential impurities based on the toxicological profile of the chemicals.

The Applicant identified a new impurity called (b) (4) which was observed to be (b) (4) fold higher in the sample from the 9-month patch compared to that of the sample from the one month patch. The genotoxicity assessment of this compound showed negative results indicating low potential for carcinogenicity.

The (b) (4) could not be detected in this study. The lower limit of detection for (b) (4) in this assay were (b) (4) ppm respectively. The Applicant set specifications of (b) (4) respectively. The toxicity assessment of (b) (4) were conducted by the reviewer based on the data available from the public literature. Carcinogenicity evaluation of the residual monomers indicates that carcinogenicity assessment of (b) (4) are only partially complete, that is the studies are either done in one species or done in two species without adequate dosages. The reviewer assessed the carcinogenicity based on the summary of data from the publicly available literature. The carcinogenicity assay conditions such as whether the carcinogenicity studies were conducted in GLP condition or not, whether the study reports were audited or not etc. are not clear. Based on all of these above mentioned reasons, the carcinogenicity potential of the monomers deemed unclear. However, it is reassuring that the Applicant could not detect the residual monomers in the current assay condition. Therefore, the reviewer recommends the specification should be closed to the lower limit of detection at which the Applicant could not detect any of these residual monomers.

The fentanyl related impurities were found in the (b) (4), some of these are identified as (b) (4).

In conclusion, the study report from the extractable/leachable study did not always identify, quantify, and provide the toxicological assessment of the potential impurities. Therefore specification of (b) (4) need to be lowered according to the manufacturing capabilities as the toxicity information of these monomers are unclear. The potential genotoxic impurities of the drug substance need to be either tested in an Ames test or their levels should be reduced ≤ 1.5 mcg/day. The safety of the potential impurities needs to be appropriately evaluated based on their toxicity assessments.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 19-813

Review number: 1

Sequence number/date/type of submission: 044 / January 30, 2009 / CMC Supplement

Information to sponsor: No

Sponsor and/or agent: ALZA Inc.

Manufacturer for drug substance: (b) (4)

Reviewer name: Mamata De, Ph.D.

Division name: Division of Anesthesia, Analgesia, and Rheumatology Products

HFD #: 170

Review completion date: July 17, 2009

Drug:

Trade name: Duragesic® CII (Fentanyl transdermal system)

Generic name: Fentanyl

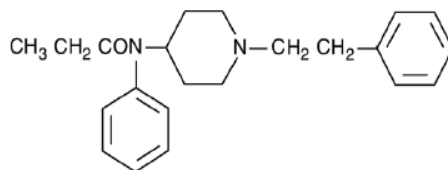
Code name: None

Chemical name: N-Phenyl-N-(1-(2-phenylethyl)-4-piperidiny) propamide

CAS registry number: 437-38-7

Molecular formula/molecular weight: C₁₂H₂₈N₂O /336.5

Structure:



Relevant INDs/NDAs/DMFs:

IND/NDA/DMF	Drug Product	Applicant	Manufacturer	Status
NDA 19-813	Duragesic® Transdermal Fentanyl Patch	ALZA Inc.	N/A	Approved 1990
IND (b) (4)	(b) (4)			
IND 46-034	Duragesic – matrix formulation	ALZA Inc.		Active
DMF (b) (4)	(b) (4)			
DMF				
DMF				
DMF				
DMF				
DMF				

Drug class: Opioid Agonist; Narcotic

Intended clinical population: Duragesic® (Fentanyl Transdermal System) is intended to be used in the opioid tolerant patient for the management of persistent, moderate to severe pain.

Clinical formulation: The Duragesic® (Fentanyl Transdermal System) would be distributed in 5 individually packaged system containing 2.1 -16.8 mg of fentanyl as indicated in the following table from the Applicant. The fentanyl patch could be ware for a maximum of 72 hrs. The amount of fentanyl released from each system/hr is proportional to the surface are (25 mcg/h/10 cm^2). The composition/ unit of all of the above mentioned sizes of the Duragesic® are identical.

Duragesic® Dose (mcg/h)	System Size (cm^2)*	Fentanyl Content (mg)**
12	5.25	2.1
25	10.5	4.2
50	21	8.4
75	31.5	12.6
100	42	16.8

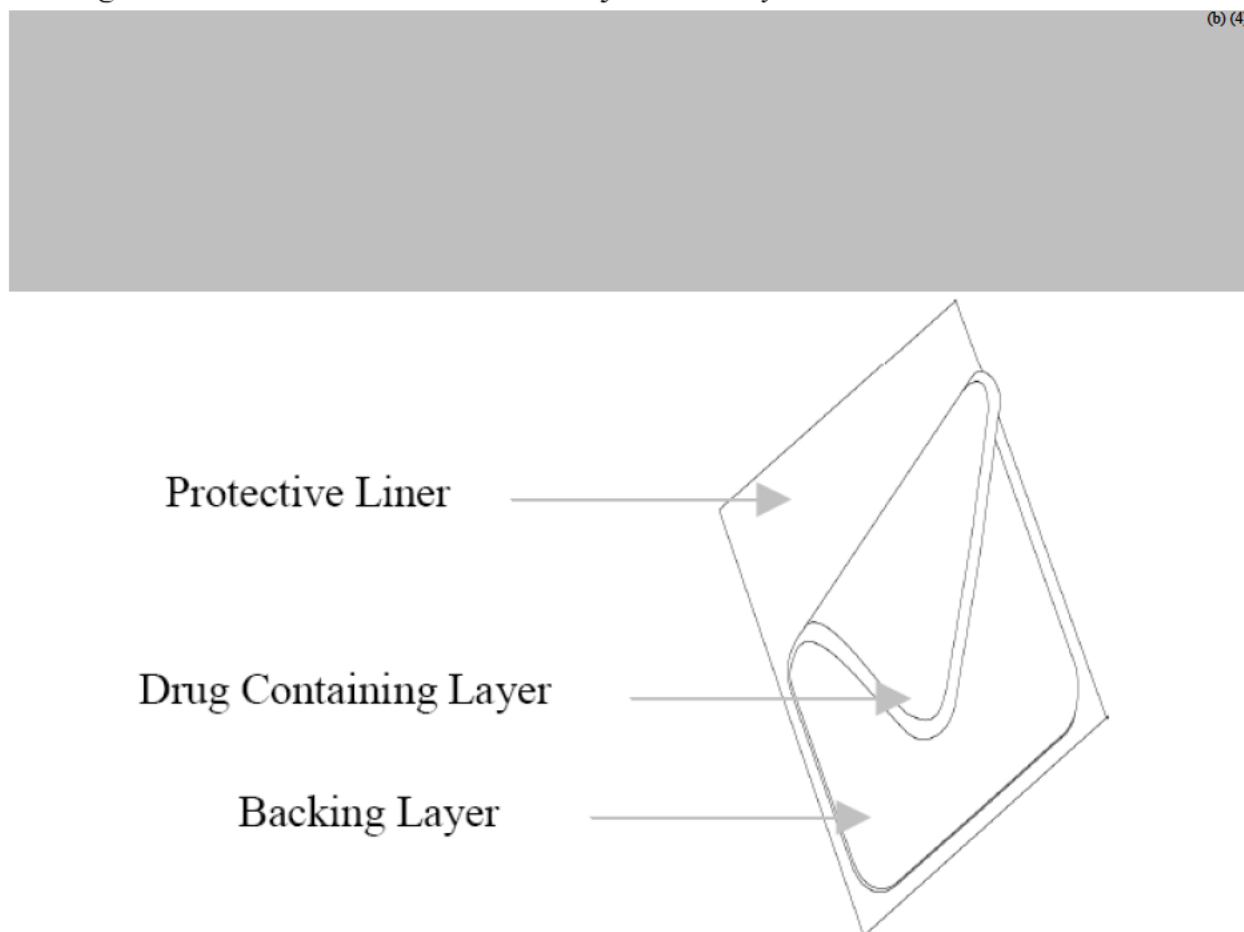
*patch sizes are different in fentanyl- gel system (original NDA 19-813) than fentanyl- matrix system (current sNDA19-813); the fentanyl content in the fentanyl in gel systems 12, 25, 50, 75, and 100 mcg/h were 5, 10, 20, 30, and 40 cm^2 respectively.

**fentanyl contents in different patches are different in fentanyl- gel system (original NDA 19-813) than fentanyl- matrix system (current sNDA19-813); that the fentanyl content in the fentanyl in gel systems 12, 25, 50, 75, and 100 mcg/h were 1.25, 2.5, 5, 7.5, 10 mg respectively.

Description of the product:

The Duragesic® (Fentanyl Transdermal System) uses matrix technology in which fentanyl base is incorporated into a pressure sensitive acrylate adhesive as described in the following schematic diagram and text from the Applicant.

Figure 3.2.P.1-A: D-TRANS® Fentanyl Matrix System



Note that DURAGESIC® is a rectangular transparent unit consisting of a backing layer, a drug containing layer, and a protective liner. The backing layer consists of (b) (4) with (b) (4) monomer (b) (4). It is used to maintain the adhesive property of the patch until it is ready to use. The protective liner is composed of (b) (4). The (b) (4) provides easy removal of the systems from the protective liner prior to use due to a (b) (4) peel force. It has (b) (4) solubility in the drug product according to the Applicant. Before use protective liner covering the adhesive layer needs to be removed and discarded. (b) (4) This excipient is novel; the toxicity evaluation of this inactive ingredient is conducted by (b) (4) and submitted to the US FDA DMF (b) (4). The Applicant submitted a 'Letter of Authorization' for using the DMF data for the evaluation of safety for this product. The toxicology information in the DMF has been reviewed (see my review of MF (b) (4) submitted July 29, 2009) and the published information on

the potential toxicity of residual monomers is summarized in the Appendix 2 of this review. The composition of the DURAGESIC® matrix is reproduced in the following table as follows from the Applicant.

Quantity Per Patch (mg per patch)							
Nominal Delivery Rate:			12 µg/h	25 µg/h	50 µg/h	75 µg/h	100 µg/h
Patch Area (cm ²):			5.25	10.5	21.0	31.5	42.0
Components	Function	Quality Standard					
Backing Layer ^a	(b) (4)						
Drug Reservoir							
Protective Liner ^b							
Inks							
Total Patch Weight							
PATCH WEIGHT WITHOUT PROTECTIVE LINER							
^c Weights shown are examples. Material added to batch as			(b) (4)				
^d Dry weight							
^e Removed during processing			(b) (4)				
			(b) (4)				
			(b) (4)				
			(b) (4)				

Impurity qualification:

D-TRANS Fentanyl Matrix Transdermal System contains potential genotoxic and non genotoxic impurities in the (b) (4). The transdermal delivery system has not been tested in any *in vitro* skin cadaver assay or *in vivo* animal model to understand the bioavailability of any of these impurities. The Applicant was recommended by the Agency to submit an extractable/leachable study report to understand the qualitative as well as the quantitative profile of the impurities from the drug product in the pre NDA meeting, July 2008. In a teleconference dated May 26th, 2009, the Applicant was reminded that in the absence of such documentation of the impurity profile, the sNDA 19-813 could not be approved. The Applicant subsequently submitted a protocol for the extractable study which was reviewed and commented on by the FDA CMC and pharmacology reviewers. The Applicant incorporated the recommendation provided by FDA and submitted the study report (PSGA Doc.-211550) of the complete drug product on July 2nd, 2009.

The extractable study was designed to identify any expected impurities arising from the individual components of the DURAGESIC® Matrix product, and any impurities that might result from possible chemical interaction between the drug substances, the adhesive layer, or other components of the drug product. Three different types of solvents such as isotonic saline, formic acid, and ethanol were used for the extraction of

any impurities from the drug product which represented normal to harshest condition for extraction. Two different temperatures were used to represent normal skin temperature (32°C) and harsher temperature (body temperature, 37°C) respectively. The extractable solutions were prepared by exposing one month and 9-month DURAGESIC® Matrix products to solvents using diffusion cells in a controlled temperature water bath. Also the sample tested included one and 9 month stability batches of the fentanyl system. The extractables from this study were identified employing HPLC (b) (4), GC (b) (4) and GC-MS technology. The extractables which were greater than that of the identification threshold were identified and assigned as new impurities which were further characterized using mass spectrometry analysis. The methodology employed and the study design is considered as a valid extractable study by the reviewer.

The Applicant identified potential fentanyl related extractables/leachables, and drug product related impurities, however, the toxicity evaluation of these leachates were not appropriately evaluated. Also, appropriate use of solvent for the extraction of the fentanyl related impurities might be necessary.

The potential drug substance impurities which were assayed and obtained from the extractable study submitted were (b) (4) (Applicant's Table 6. PSGA-Doc-211550). Of these, (b) (4) are considered to contain a (b) (4). The Applicant set a specification for (b) (4) for the Impurity (b) (4) which is equivalent (b) (4) mcg/day (b) (4) patches wore in an opioid tolerant patient, each patch containing (b) (4) mg). This specification is in compliance with the DRAFT CDER Guidance on the qualification of genotoxic impurities which set the limit for genotoxic impurities at the level of NMT 1.5 mcg/day. There are other fentanyl-related potential genotoxic impurities such as (b) (4) which were identified and quantified in the current extractable/leachable study. There might be other fentanyl related impurities which were not detected because of the limitation of the current study protocol. Therefore, the Applicant submitted a protocol for detecting all the extractables from the drug substance (Protocol number PSGA 210122) which will use phosphoric acid as a solvent for extraction of the entire fentanyl related product). The reviewer strongly recommends that the potential genotoxic impurities identified from the current study either be tested in the Ames assay for mutagenicity or the limits of these impurities be reduced to 1.5 mcg/day. Because these impurities are already present in the marketed product, the qualification of these genotoxic impurities need to be conducted as a post marketing commitment. (b) (4) which has also been found as an extractable in this study should be limit to (b) (4) mcg/day according to the toxicity findings assessed by other government regulatory bodies such as EPA.

In an effort to profile any (b) (4) and other impurities which may extract or leach out of the drug product, the Applicant conducted assays for (b) (4)

(b) (4) could not be detected using the methods employed in the current study. Also, the reference materials for (b) (4) were not available; therefore these potential leachables were not quantified. The GCMS analyses could not detect (no peak/s) appreciable amount of any of these parent ions which suggests that under this experimental condition, only a very little amount of the above mentioned product might be present. The toxicological assessments of these potential leachates are insufficient. The (b) (4) are known to cause CNS depression, testicular damage, carcinogenicity potential for these compounds are not known (b) (4). The Applicant did not find any appreciable toxicological profile of (b) (4); the publicly available database did not provide any assessment of toxicity for these compounds indicating that the toxicity of this compound is not clearly understood. The (b) (4) compounds such as (b) (4) are well known mutagenic carcinogen, (b) (4) if present as leachates may act as a plausible precursor of toxic (b) (4) compounds. All of these information led the reviewer to recommend that the leachable study with the protocol #PSGA number (b) (4) executed by the Applicant should be conducted to characterize all of these compounds to evaluate the toxicity of these potential leachates.

The (b) (4) of the (b) (4) reaction and its byproduct/s are anticipated to be present in the drug product. The (b) (4) reaction was initiated by (b) (4) is used as (b) (4) for components of paper and paperboard in contact with food (b) (4) and for cross-linking (b) (4) intended for repeated use in contact with food provided the (b) (4) content does not exceed (b) (4) weight percent (b) (4) ppm) of the finished resin (b) (4). Residual levels of (b) (4) at the end of the (b) (4) process, however, estimated using a theoretical calculation based on (b) (4) thermal stability (half-life). Based on this calculation the manufacturer estimated that (b) (4) ppm of (b) (4) might be remaining in the adhesive at the end of manufacturing process. At this level, (b) (4) does not pose any indication for health hazard. The current study result noted that LOD for (b) (4) is approximately (b) (4) ppm, indicating that methods need to be improved to detect (b) (4) in a more sensitive assay.

(b) (4) has been identified as a by- product of the (b) (4) (b) (4) is a neurotoxicant; the threshold limit of (b) (4) is identified as (b) (4) ppm by NIOSH. Because of its high volatility (b) (4), however, the level of (b) (4) in the (b) (4) adhesive film will depend on conditions used such as (b) (4) temperature, coating thickness etc. The supplier (b) (4) developed a validated method for identifying the residual (b) (4). The Applicant may need to adopt the method to estimate (b) (4) contain of the drug product. The specification for (b) (4) needs to be (b) (4) ppm.

The level of the three residual monomers namely (b) (4) were below the limit of detection.

The specification set by the Applicant for (b) (4) ppm respectively (refer to the following table).

Residual Monomers	Extractable/100 mcg patch*	Specification Limit
(b) (4)		

*LOD= Limit of Detection

The toxicity assessment of (b) (4) were conducted by the reviewer based on the data available from the public literature and discussed in detail in the Appendix 2.

Three carcinogenicity studies using (b) (4) have been identified which demonstrated carcinogenicity findings in mice. In one of those studies, solutions of (b) (4) % (b) (4) in acetone were topically applied to a group of 80 male mice 3 x/week throughout their life time. No neoplasms were observed at 2.5 % group (approximately 625 µg/day). With (b) (4) % (b) (4) severe skin irritation was associated with benign and malignant skin tumors, hyperkeratosis, scabs, thickened subcutaneous tissue, papillomas, cornified squamous cell carcinomas, malignant melanomas, fibrosarcomas, and dermal hyperplasia. All these findings suggest that the carcinogenicity findings might be secondary to irritation and not due to the direct effect of (b) (4). In another carcinogenicity study with (b) (4) % (b) (4) in acetone when applied topically in male mice for 6- months, 2/40 treated animals developed squamous cell carcinomas and 4/40 treated animals showed squamous cell papillomas. In an additional study, (b) (4) % (b) (4) solution in acetone when topically applied in mice (male, 40/group), 2/40 developed malignant skin carcinoma; 1/40 from the vehicle control group had similar findings. All these carcinogenicity findings identify (b) (4) as a hazardous material at high dose. An embryo-fetal toxicity study conducted in Sprague Dawley rats exposed to (b) (4) from gestation days 6-20 showed >10% decrease in maternal body weight at 100 ppm, but not with 50 and 70 ppm dosages. No teratology findings were noted in this study.

(b) (4) was observed to produce carcinomas in nasal cavity in the inhalation study in rat and mouse carcinogenicity bioassay and was classified by IARC as Class (b) (4) carcinogen and considered by the Agency as a 'site of contact' carcinogen in rodents. Note that (b) (4) was observed to be not mutagenic, but was positive in the clastogenicity studies such as sister chromatid exchange assay most probably due to the formation of its major metabolite acetaldehyde. A two year carcinogenicity study in rats via the inhalation route of exposure demonstrated no signs of proliferation or irritation at (b) (4) ppm (b) (4) µg/cm²/day).

Genotoxicity studies with (b) (4) revealed that it is not mutagenic without metabolic activation in the Ames test. (b) (4), however, was observed to be positive (b) (4) fold

increase in revertants as compared to controls) at (b) (4)

(b) (4) also reported a dose related increase (0, 15, 18, and 20 µg/ml concentrations tested) in chromosomal aberrations and micronuclei in L5178Y mouse lymphoma cells treated with (b) (4) in the absence of metabolic (b) (4) activation. An inhalation carcinogenicity study in rat produced a NOAEL of (b) (4) ppm in rat.

Carcinogenicity evaluation of the residual monomers indicates that carcinogenicity evaluation of (b) (4) are only partially complete. NOAEL for carcinogenicity have been determined from only one of the two species recommended by the ICH Guidelines. The reviewer assessed the carcinogenicity based on the summary of data from the publicly available literature. The carcinogenicity assay conditions such as whether the carcinogenicity study was conducted in GLP condition or not, whether the study report was audited or not etc. not clear. Based on all of these above mentioned reasons, the carcinogenicity potential of the monomers deemed unclear. However, it is reassuring that the Applicant could not detect the residual monomers in the current assay condition. Therefore, the reviewer recommends the specification should be closed to the lower limit of detection at which the Applicant could not detect any of these residual monomers.

On the process of identifying the new impurities using the current assay condition, the Applicant identifies a peak in their GC-MS analyses which was subsequently characterized as (b) (4). The compound is listed as (b) (4) agent in 21-CFR and predicted as safe up to the 0.65 mcg/kg body weight. (b) (4) was observed to produce hepatocarcinoma in mice in a human equivalent dose of 16 mg/kg (b) (4). This compound was observed to increase (b) (4) fold in the patch prepared for a longer duration of time (9-month patch) compared to the patch prepared recently with all of the extractable solvents. Therefore the limit of the (b) (4) appeared to be specified in the current formulation of the fentanyl patch.

Additional potential extractables identified by the Applicant in this study were

(b) (4), however, the assay methods could only quantify the above mentioned chemicals to the levels of (b) (4) ppm respectively which are their lower limit of detections. The toxicity information of these chemicals was not appropriately synthesized by the Applicant. The publicly available literature evaluated by the reviewer, showed (b) (4) has been used in different skin ointments as antioxidant and may pose little concern for toxicity; however, (b) (4) need to be evaluated for toxicity. The Applicant should summarize the toxicity information and establish specification for these compounds if necessary.

In conclusion, the study report from the extractable/leachable study did not always identify, quantify, and provide the toxicological evaluation of the potential impurities; therefore qualification of these impurities is necessary. The specification of (b) (4) need to be lowered according to the

manufacturing capabilities as the toxicity information of these monomers are unclear. The potential genotoxic impurities of the drug substance need to be either tested is Ames test or their levels should be reduced ≤ 1.5 mcg/day. Note that the toxicity evaluation of the (b)(4) is evaluated from the publicly available literature (Appendix 2).

Route of administration: Transdermal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Study no.	Study title
TR-02-5715-035	A Primary Skin Irritation Study of D-TRANS [®] (fentanyl) Systems with Naltrexone HCl/EVA-28 in Hairless Guinea Pigs
TR-03-5716-001	A Primary Skin Irritation Study of D-TRANS [®] Fentanyl systems in Hairless Guinea Pigs
TR-02-5715-037	Study title: Subchronic Skin Irritation Study using D-TRANS [®] (Fentanyl) systems with Naltrexone HCl/EVA-28 in Hairless Guinea Pigs
TR-02-5715-036	Evaluation of the Sensitization Potential in Guinea Pigs of D-TRANS [®] Fentanyl Systems with Naltrexone HCl

Studies not reviewed within this submission: All submitted studies were reviewed.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Fentanyl is a synthetic opioid agonist that interacts primarily with the u-opioid receptor subtype to produced analgesia and sedation. It increases the patient's tolerance for pain and decreases the perception of suffering, although the patient may still recognize the pain itself. Opioids work to relieve nociceptive pain but are not very effective for neuropathic pain. In addition to analgesia mu-opioid agonists such as fentanyl produce drowsiness, changes in mood, respiratory depression decreased gastrointestinal motility, nausea, vomiting and alterations in the endocrine and autonomic nervous system.

2.6.2.2 Primary pharmacodynamics

No new information was submitted with this NDA.

2.6.2.3 Secondary pharmacodynamics

High doses of fentanyl produce muscle rigidity possibly due to effects of opioids on dopaminergic transmission in the striatum. The euphoric effects of opioids are believed to be mediated in part via interaction with opioid receptors located in the ventral tegmental area (VTA) leading to the enhancement of dopamine release in the nucleus accumbens. Opioid receptors in the locus coeruleus appear to inhibit the adrenergic neurons thought to play a role in feelings of alarm, panic, fear and anxiety. Opioids act within the hypothalamus to regulate body temperature (generally temperature decreases slightly, but at higher doses temperature may increase). Opioids inhibit neuroendocrine systems including gonadotropin-releasing hormone (GNRH) and corticotropin-releasing factor (CRF) thereby decreasing release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenal corticotrophic hormone (ACTH), and P-endorphin. This leads to decrease plasma levels of testosterone and cortisol. Opioids increase circulating levels of prolactin. Opioids such as fentanyl lead to constriction of the pupil (miosis) via increased parasympathetic nerve activity innervating the pupil. Pinpoint pupils are pathognomonic for toxic doses of μ -opioid agonists; however mydriasis can develop upon asphyxia.

No new pharmacology study with fentanyl was submitted with the current NDA.

2.6.2.3 Safety pharmacology

The safety of fentanyl administration pertaining to the submitted NDA is similar to those following systemic administration of potent opioids. The major concern is respiratory depression, which can occur at plasma concentrations between 2 and 4 ng/ml. In addition, fentanyl administration may produce sedation, nausea and vomiting, bradycardia, urinary retention and constipation. Although opioids such as fentanyl can have significant safety concerns, the effects are well known. Therefore, given careful clinical monitoring, especially for respiratory depression, the proposed application does not appear to pose significant concerns regarding safety pharmacology.

Opioids are readily absorbed from the gastrointestinal tract and the rectal mucosa. More lipophilic agents are also absorbed through the nasal or buccal mucosa and those with the greatest lipophilicity can be absorbed transdermally. An increase in temperature from 32°C to 37°C has been shown to double the rate of fentanyl delivery.

No new safety pharmacology study with fentanyl was submitted with the current NDA.

2.6.2.5 Pharmacodynamic drug interactions

There was no nonclinical pharmacodynamics studies submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Fentanyl is widely distributed in the body following its administration. There is some evidence that it can accumulate in skeletal muscle and fat. Fentanyl demonstrates approximately 69-84% protein binding and an average volume of distribution of 6 L/kg. Fentanyl crosses the placenta and can also be detected in breast milk. Fentanyl is metabolized primarily in the liver by N-dealkylation and hydroxylation via cytochrome P450 3A4. In humans, the primary metabolite is nor fentanyl. Fentanyl is not considered to have any active or toxic metabolites.

The metabolites of fentanyl and unchanged drug are primarily eliminated via the urine with only 10% representing the unchanged drug. About 9% of the dose is eliminated in the feces, primarily as metabolites. The skin does not appear to metabolize fentanyl that is absorbed transdermally.

2.6.4.2 Methods of Analysis

There was no nonclinical ADME studies submitted with the current NDA. Therefore no method of analyses was provided with the current submission.

2.6.4.3 Absorption

There was no nonclinical absorption studies submitted.

Various in vitro and in vivo studies on topical application in animal species have already established that transdermal dosing of fentanyl is feasible. Non-ionized fentanyl showed a relatively high penetration through the lipid-rich stratum corneum, but the viable skin appeared to be a stronger barrier to absorption. No indications for fentanyl metabolizing activity in the skin were present, suggesting that fentanyl was absorbed through the skin unchanged.

2.6.4.4 Distribution

There was no nonclinical distribution studies submitted. Plasma protein binding and distribution studies with fentanyl in blood showed that there were no major species. The binding amounted to 69% in mice, 83% in rats, 74% in rabbits, 78% in dogs and 84% in man. In whole blood of rat, dog and man, fentanyl present in the plasma water fraction was 17%, 16% and 17%, respectively. Plasma protein binding was not concentration-dependent and appeared to be based on hydrophobic interaction. Albumin was the major, but not the only, binding protein in human plasma: binding to α_1 -acid glycoprotein and to lipoproteins was also observed. Animal and human blood levels were comparable to plasma levels. The uptake of fentanyl by red blood cells appeared to be a linear function of the free drug concentration in plasma and hemoglobin was the major binding site in human erythrocytes.

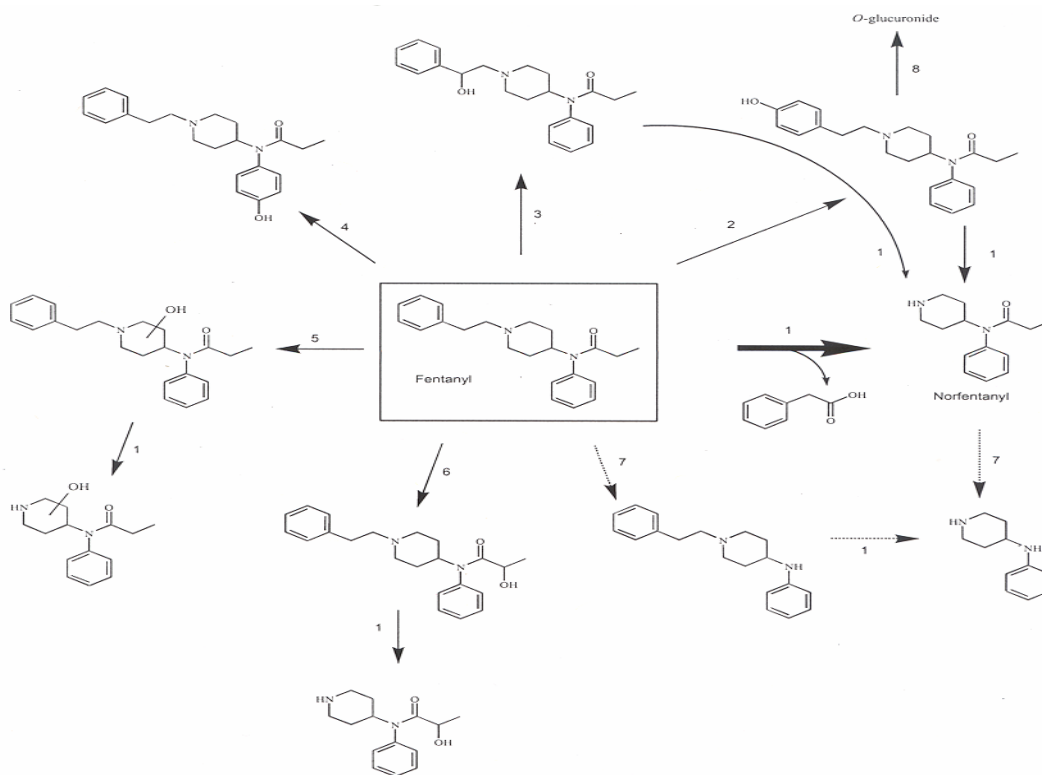
In all animal species studied, the fast onset as well as the short duration of the effect of fentanyl after intravenous administration was ascribed to the very pronounced and rapid uptake of the drug in brain followed by a rapid redistribution to sites of storage (muscle and fat) and biotransformation (liver). Rat tissue-to-plasma partition coefficients for fentanyl

were >20 in fat, spleen and pancreas, >10 in lung, kidney and stomach, >5 in small intestine and testis, >2 in brain, heart, liver, large intestine, muscle and skin. In the dog, fentanyl levels in cerebrospinal fluid were approximately half those in plasma and this concentration difference was ascribed to plasma protein binding. In mouse, rabbit, sheep and man, passage of the placenta was limited. In sheep, fentanyl did not induce alterations in uterine tone or uterine blood flow.

2.6.4.5 Metabolism

There was no nonclinical metabolism studies submitted. The main metabolic pathway of fentanyl in animals and man is the oxidative N-dealkylation to norfentanyl, with the possible exception of the dog. In addition, metabolites are formed via aromatic as well as aliphatic hydroxylation. Amide hydrolysis appears to be a minor pathway or does not occur at all. The narcotic analgesic activity of fentanyl can be ascribed to unchanged drug.

Metabolic pathways of fentanyl in animals and man (following diagram): 1: oxidative N-dealkylation, 2: aromatic para-phenyl hydroxylation, 3: aliphatic (x-phenylethyl oxidation), 4: aromatic aniline hydroxylation, 5: piperidine oxidation, 6: aliphatic (co-l)-propionyl oxidation, 7: amide hydrolysis (minor pathway, if present), 8: O-glucuronidation



2.6.4.6 Excretion

Renal clearance of fentanyl is low. Fentanyl metabolites formed are eliminated both in urine and in feces.

2.6.4.7 Pharmacokinetic drug interactions

Based on in vitro data, CYP3A4 is the major human P450 isoform involved in the main metabolic route for fentanyl, the oxidative N-dealkylation to norfentanyl. In vitro interaction data indicated that several drugs were able to inhibit the metabolism of fentanyl. However, the clinical relevance of these in vitro findings is probably limited to the more potent inhibitors of the fentanyl metabolism because fentanyl is a high-clearance compound, relatively insensitive to changes in intrinsic clearance. Itraconazole, for example, which is a very potent inhibitor of fentanyl metabolism in vitro, was studied in vivo in healthy subjects and resulted in no statistically significant change in the clearance of fentanyl. Therefore it is expected that only even more potent inhibitors of fentanyl metabolism, such as ketoconazole and ritonavir, may have a clinically relevant influence on fentanyl clearance.

2.6.4.8 Other Pharmacokinetic Studies

There was no nonclinical pharmacokinetics studies submitted.

2.6.4.9 Discussion and Conclusions

The Applicant did not submit any new non clinical ADME data with the NDA. Duragesic® (Fentanyl Transdermal Matrix System) is a new transdermal formulation, however, fentanyl transdermal application in gel formulation is a FDA approved, marketed product. No safety issues as regards to the ADME profile had so far been identified clinically with the transdermal gel formulation. The matrix formulation has new excipients; however, the excipients are not expected to cross react with the active ingredients and its metabolites. Therefore no changes in the safety profile associated with ADME are expected with the current fentanyl formulation.

2.6.4.10 Tables and figures to include comparative TK summary: NA

2.6.5 PHARMACOKINETICS TABULATED SUMMARY: NA

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The Applicant relied on marketed Duragesic® reservoir for the nonclinical safety assessment. The reviewer agreed on the safety assessment of fentanyl based on the above mentioned product. The safety of the novel excipient was assessed based on the toxicity

data of (b) (4) submitted with the DMF and the toxicity data available from the literature which is summarized in Appendix 1.

To evaluate local toxicity, the Applicant submitted an acute (72-hrs) irritation study in guinea pigs, a 21-day sub chronic irritation study in guinea pigs, and a sensitization study in guinea pig. In these studies, fentanyl patches were used topically in guinea pig, the composition of the patches is comparable to those of the patches which would be used clinically except that an extra compartment with naltrexone (NTX) was added to the non clinical patch. This NTX compartment is believed not to have any interference with the fentanyl efflux. No primary irritation or sensitization was observed in the non clinical species, however, mild cumulative irritation was observed in the subchronic studies with all of the patches including vehicle control, indicating that the patch component itself is irritating. Skin histology from the irritation studies showed increase lesions in animals treated with patches containing fentanyl. These lesions consist of parakeratosis and inflammation with increase in macrophage infiltration. The Applicant also conducted an acute primary irritation study in guinea pigs (72-hrs) using transdermal patch exactly similar to the clinical patches. No primary irritation was observed in these studies.

2.6.6.2 Single-dose toxicity

There was no nonclinical single dose toxicity studies submitted.

2.6.6.3 Repeat-dose toxicity

There was no repeat dose toxicity studies submitted.

2.6.6.4 Genetic toxicology

There was no genetic toxicology studies submitted with the current NDA. The label from the Duragesic gel formulation reads that there is no evidence of mutagenicity in the Ames *Salmonella* mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration in-vitro assay. Currently, there is no need to change the labeling for the genetic toxicity section for the sNDA submitted.

2.6.6.5 Carcinogenicity

The Applicant submitted the fentanyl subcutaneous carcinogenicity study report in rat; this study is reviewed and attached in the Appendix 2 along with the ECAC review summary.

2.6.6.6 Reproductive and developmental toxicology

There were no reproductive toxicity studies submitted with the current NDA. According to the reviewer no labeling change is required for the current product for this particular section. The fertility and pregnancy section of the current Duragesic label reads as follows:

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/m² 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 – 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 µg/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/m² 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/m² basis).

There are no adequate and well-controlled studies in pregnant women. DURAGESIC® 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 of 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/m² basis.

Labor and Delivery

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

2.6.6.7 Local tolerance

Study title: A Primary Skin Irritation Study of D-TRANS[®] (fentanyl) Systems with Naltrexone HCl/EVA-28 in Hairless Guinea Pigs**Key study findings:**

- The purpose of this study was to evaluate the safety of the 1 cm² D-TRANS system (transdermal patch) which contains either fentanyl (0.4 mg) and naltrexone (1.5 mg) in different compartments or naltrexone alone (1.5 mg) or no fentanyl and naltrexone (vehicle).
- To evaluate the safety six hairless guinea-pigs were applied with the patches topically on the intact dorsal skin for 96 hours and the primary irritation index, the skin histology were assessed for 48 hrs post patch removal.
- The study appeared to show no irritation in 3/6 animals, in 1/6 animals the primary irritation index(PII) could not be confirmed due to the fact that no patch was observed at the end of the study, and in 2/6 animals erythema and edema was observed 48 hrs post dosing.
- The skin histology assessment revealed increase inflammation in the dermis in all D-TRANS treated skin compared to that of the naïve skin. One of the animals in which D-TRANS w/fentanyl treated skin showed PII also showed inflammation of the panniculus (adipose tissue). This finding was characterized by infiltration of macrophages, lymphocytes, and neutrophils in the panniculus. The Applicant does not consider it as treatment related because there were no inflammatory changes in the tissue between panniculus and superficial dermis.
- Reviewers noted that the patches containing naltrexone were used in the study; therefore, the study design did not mimic the clinical application where no naltrexone is present in the transdermal patch. However the data appear to show fentanyl related increase in skin irritation and severity in the histology findings.
- The residual drug analyses from the patch showed that 0.11 mg fentanyl was released over the 96 hr application period which is equivalent to 1.15 µg/cm².hr.

Study no.: TR-02-5715-035**Volume # and page #:** Module 2 eCTD submission; pages 1-77**Conducting laboratory and location:** ALZA Corp.; Mountain View, CA**Date of study initiation:** October 17, 2002**GLP compliance:** Yes**QA reports:** Yes**Drug, vehicle, lot #, and purity:** Following products were tested in the current study:**Drug:** 1 cm² D-TRANS[®] (w/fentanyl, w/naltrexone);**Vehicle:** 1 cm² D-TRANS[®] (wo/fentanyl, wo/naltrexone);**Control:** 1 cm² D-TRANS[®] (wo/fentanyl, w/naltrexone);

Fentanyl and naltrexone content of each formulation are reproduced from the Applicant's table A as follows.

Table A: Test and Control Systems

D-TRANS [®] system (1 cm ² each)	Content	
	Fentanyl Base	Naltrexone Base
D-TRANS [®] (w/o fentanyl, w/o naltrexone) NB# 7223:39-40, 7011:99-100	0 mg	0 mg
D-TRANS [®] (w/o fentanyl, w/ naltrexone HCl) NB# 7223:39-41, 7011:102, 109	0 mg	1.5 mg
D-TRANS [®] (w/ fentanyl, w/ naltrexone HCl) NB# 7223:39-42, 7011:99-100, 102, 109	0.4 mg	1.5 mg

A schematic diagram of the D-TRANS[®] system is reproduced as follows from the Applicant's submission. Briefly, D-TRANS[®] system is composed of a protective liner

(b) (4) [REDACTED] a barrier layer (b) (4)
[REDACTED] another (b) (4)
(b) (4) and a (b) (4) backing layer. Note that (b) (4) is a
(b) (4) which is a novel excipient.

are reproduced as follows from the submission.

FIGURE 1: D-TRANS® System Formulation and Schematic Diagram

Methods

Doses: One dose of the active ingredient (0.4 mg) was used as shown in Applicant's table A. The study scheme is reproduced as follows.

FIGURE 2: Study Schema

Study Day	Date	Task
0	4/4/03	Guinea pig BW/CO; test article application, bandage/animal check
1	4/5/03	Bandage/animal check
2	4/6/03	Bandage/animal check
3	4/7/03	Bandage/animal check
4	4/8/03	Test article removal, 30-40 min post-removal scoring
5	4/9/03	24-hour post-removal scoring
6	4/10/03	48-hour post-removal scoring; guinea pig BW/CO; guinea pig euthanasia

Note: BW/CO = body weights and clinical observations

Study design: Six female hairless guinea-pigs (strain IAF: HA-HO- hr) were used in this study. Each of the six guinea pigs had three different D-TRANS® system (w/fentanyl wo/naltrexone, w/fentanyl w/naltrexone, and wo fentanyl wo/naltrexone) applied topically to three different areas on the intact dorsal skin for approximately 96 hours.

The site of applications were cleaned with alcohol and dried prior to the application of the D-TRANS system. The dosing plan is reproduced as follows from the Applicant's study design.

FIGURE 3: Dosing Plan

<u>HEAD</u>			<u>HEAD</u>			<u>HEAD</u>		
I			II			III		
Guinea Pig (06)			Guinea Pig (14)			Guinea Pig (32)		
<u>HEAD</u>			<u>HEAD</u>			<u>HEAD</u>		
A	B		C	A		B	C	
		C		B				A
Guinea Pig (42)			Guinea Pig (74)			Guinea Pig (84)		
<u>HEAD</u>			<u>HEAD</u>			<u>HEAD</u>		
A	B		C	A		B	C	
		C		B				A

A = D-TRANS® (w/o fentanyl, w/o naltrexone)
 B = D-TRANS® (w/o fentanyl, w/ naltrexone HCl)
 C = D-TRANS® (w/ fentanyl, w/ naltrexone HCl)

The application sites were scored for erythema, eschar, and edema at 30-40 min, 24 hrs, and 48 hrs following Draize's method. Following is the Attachment # 3, reproduced from the Applicant's submission which described the scoring.

ATTACHMENT 3: Evaluation of Skin Reactions
Draize et al 1944, 16 CFR 1500.41
(Page 1 of 1)

1. <u>Erythema and Eschar Formation</u>	<u>Value</u>
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Total possible erythema score	4
2. <u>Edema Formation</u>	
No edema	0
Very slight edema (barely perceptible).....	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4
Total possible edema score	4
Total possible score for primary irritation	8

Primary irritation index (PII) was calculated for each formulation. The maximum primary irritation index was calculated by adding the erythema and edema scores at the 30-40 mins, 24 hrs, and 48 hrs observation and dividing it by the number of observations. The irritation potential of the test system was categorized according to Pravo et al 1996 as follows (Applicant's table B).

TABLE B: Primary Irritation Categories

Irritation Index	Category
0-0.5	None to Negligible
0.6-2.0	Mild
2.1-5.0	Moderate
5.1-8.0	Severe

The treated skin tissues were subjected to the histological evaluation.

The Applicant also evaluated the residual drug (fentanyl and naltrexone) by analyzing fentanyl and naltrexone from the intact and worn D-TRANS matrix along with the evaluation of primary irritation index of individual animals. The Applicant also studied the histopathology of the skin tissues on which the D-TRANS matrix was applied.

Results: Residual drug analyses data showed (Applicant's table #s 5) that the estimated release of fentanyl from the worn out patches were 0.11 mg for 96 hrs of the experimental period. This corresponds to a skin flux of $1.15 \mu\text{g}/\text{cm}^2/\text{hr}$. Considering that the guinea pig's body weights were 0.7 kg in average, the approximate maximum dose of fentanyl was 0.16 mg/kg. The approximate naltrexone release from the new and worn D-TRANS with fentanyl and with naltrexone (Applicant's table # 4) was 0.09 mg. The approximate naltrexone release from the worn D-TRANS without fentanyl and with naltrexone (Applicant's table # 4) was 1.3 mg. The Applicant believes that this difference is not significant because of the data variability. The reviewer observed that the standard deviations are tighter in the data from table # 5 compared to those of the table # 4 indicating that the Applicant's conclusion on naltrexone release from the D-TRANS system might be right. However, the possible neutralizing effect of fentanyl and naltrexone when contained in the same patch could not be eliminated which might also be one of the reasons for the data variability. The Applicant's clinical formulation for the D-TRANS system do not contain naltrexone, therefore neutralization would not pose any problem clinically.

TABLE 5: D-TRANS® Fentanyl Content Data

Before in-life			After in-life			Worn		
AR no.	n	mg/1 cm ² system	AR no.	n	mg/1 cm ² system	AR no.	n	mg/1 cm ² system
D-TRANS® (w/o fentanyl, w/o naltrexone)								
48282	10	0.0	48295	10	0.0	N/A	N/A	N/A
Mean±SD		0.0±0.0	Mean±SD		0.0±0.0	Mean±SD		N/A
D-TRANS® (w/o fentanyl, w/ naltrexone HCl)								
48284	10	0.0	48286	25	0.0	48286	6	0.0
Mean±SD		0.0±0.0	Mean±SD		0.0±0.0	Mean±SD		0.0±0.0
D-TRANS® (w/ fentanyl, w/ naltrexone HCl)								
SS3699	5	0.398	SS3699	5	0.397	48285	6	0.29
(1 month)		0.399	(3.5		0.398			0.29
		0.400	months)		0.397			0.28
		0.394			0.401			0.31
		0.399			0.400			0.30
		N/A			N/A			0.26
Mean±SD		0.3980±0.0023	Mean±SD		0.3986±0.0018	Mean±SD		0.288±0.017
Estimated fentanyl release (mg) = (mean of before and after in-life – mean of worn) = 0.110								
N/A = not applicable								

TABLE 4: D-TRANS® Naltrexone Content Data

Before in-life			After in-life			Worn		
AR no.	n	mg/1 cm ² system	AR no.	n	mg/1 cm ² system	AR no.	n	mg/1 cm ² system
D-TRANS® (w/o fentanyl, w/o naltrexone)								
48282	10	0.0	48295	10	0.0	N/A	N/A	N/A
		Mean±SD			Mean±SD			Mean±SD
		0.0±0.0			0.0±0.0			N/A
D-TRANS® (w/o fentanyl, w/ naltrexone HCl)								
48284	10	0.86	48286	25	1.14	48286	6	0.85
		1.18			1.16			0.93
		1.12			1.03			0.89
		0.88			1.05			0.78
		1.11			1.13			1.12
		N/A			N/A			1.07
		Mean±SD			Mean±SD			Mean±SD
		1.030±0.149			1.102±0.058			0.940±0.131
Estimated naltrexone release (mg) = (mean of before and after in-life – mean of worn) = 0.126								
D-TRANS® (w/ fentanyl, w/ naltrexone HCl)								
SS3699	5	1.59	SS3699	5	1.46	48285	6	1.50
(1		1.70	(3.5		1.51			1.44
month)		1.53	months)		1.70			1.57
		1.59			1.77			1.39
		1.56			1.43			1.44
		N/A			N/A			1.62
		Mean±SD			Mean±SD			Mean±SD
		1.594±0.064			1.574±0.152			1.493±0.088
Estimated naltrexone release (mg) = (mean of before and after in-life – mean of worn) = 0.091								

N/A = not applicable

Primary irritation index of individual animals are reproduced in the following tables from the Applicant. The Applicant observed that the mean primary irritation index (PII) was between 0.3-0.4 which is negligible considering the PII categorized by Prevo et al. The reviewer noted that in 3/6 guinea pigs erythema and edema were recovered by 48 hrs. However, in three other animals, that is in 50 % of the animals either the irritation could not be scored (animal #s 42 and 32) or there were persistent irritation at least for 48 hrs (Animal # 14). In 1/6 (animal #32) the D-TRANS patch w/fentanyl and w/animals naltrexone could not be scored because there was no sign of the patch. In another animal the irritation was scored because the patch was found shrink to one end (animal # 42) indicating that the animals might not be appropriately exposed to the drug. Animal #s14 and 42 indicated irritation at 48 hrs with D-TRANS containing naltrexone only. The result indicated that these two animals might be more susceptible to the application of the patch.

TABLE 2: Skin Irritation Data Summary

(Page 1 of 3)

1 cm² D-TRANS[®] (w/o fentanyl, w/o naltrexone)

Score Time		Guinea Pig Number (Application Site)					
		06(I)	14(II)	32(III) ^a	42(I)	74(II)	84(III)
0.5 Hour	Erythema	0	0	N/A	1	0	1
	Edema	0	0	N/A	0	0	0
	Total, Erythema+Edema	0	0	N/A	1	0	1
24 Hour	Erythema	0	1	N/A	0	0	1
	Edema	0	0	N/A	0	0	0
	Total, Erythema+Edema	0	1	N/A	0	0	1
48 Hour	Erythema/Edema	0	1	N/A	0	0	0
		0	0	N/A	0	0	0
	Total, Erythema+Edema	0	1	N/A	0	0	0

^aNo system on animal at time of article removal. Site not visible, therefore not scored.
N/A = not applicable

$$\text{Primary Irritation Index} = \frac{\text{Sum of scores at 0.5 hour and 48 hour}}{\text{Number of observations}} = \frac{3}{10} = 0.3$$

TABLE 2: Skin Irritation Data Summary

(Page 2 of 3)

1 cm² D-TRANS[®] (w/o fentanyl, w/ naltrexone HCl)

Score Time		Guinea Pig Number (Application Site)					
		06(II)	14(III)	32(I)	42(II)	74(III)	84(I)
0.5 Hour	Erythema	0	0	0	1	1	0
	Edema	0	0	0	1	0	0
	Total, Erythema+Edema	0	0	0	2	1	0
24 Hour	Erythema	1	0	0	1	0	0
	Edema	0	0	0	0	0	0
	Total, Erythema+Edema	1	0	0	1	0	0
48 Hour	Erythema	0	1	0	1	0	0
	Edema	0	0	0	0	0	0
	Total, Erythema+Edema	0	1	0	1	0	0

$$\text{Primary Irritation Index} = \frac{\text{Sum of scores at 0.5 hour and 48 hour}}{\text{Number of observations}} = \frac{5}{12} = 0.4$$

1 cm² D-TRANS[®] (w/ fentanyl, w/ naltrexone HCl)

Score Time		Guinea Pig Number (Application Site)					
		06(III) ^a	14(I)	32(II)	42(III) ^b	74(I)	84(II)
0.5 Hour	Erythema	1	1	0	0	0	0
	Edema	0	0	0	0	1	0
	Total, Erythema+Edema	1	1	0	0	1	0
24 Hour	Erythema	0	1	0	0	1	0
	Edema	0	0	0	0	0	0
	Total, Erythema+Edema	0	1	0	0	1	0
48 Hour	Erythema	0	0	0	0	0	0
	Edema	0	0	0	0	0	0
	Total, Erythema+Edema	0	0	0	0	0	0

^a System not on site at removal time, however site location was visible and therefore scored.^b At removal time, the system was found curled up, only partially touching the skin site. Since skin site was visible, it was scored.

$$\text{Primary Irritation Index} = \frac{\text{Sum of scores at 0.5 hour and 48 hour}}{\text{Number of observations}} = \frac{3}{12} = 0.3$$

Histopathologies of the skins were analyzed by the

(b) (4)

The findings are reproduced as follows from the Applicant's table.

N

(b) (4)

Page 1

**A PRIMARY SKIN IRRITATION STUDY OF D-TRANS (FENTANYL) SYSTEMS
WITH NALTREXONE HCl/EVA-28 IN HAIRLESS GUINEA PIGS
ALZA CORPORATION STUDY NUMBER: TR-02-5715-035**

PROJECT SUMMARY

STUDY ID : D-TRANS IN PIGS

STUDY NUMBER: TR02571

FATE: ALL

HOURS ON TEST: ALL

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:	1
NUMBER OF ANIMALS:	6

D TRANS A	# EX	5
INFLAMMATION, ACUTE, DERMIS		5
INFLAMMATION, SUBACUTE, DERMIS		5
INFLAMMATION, HAIR FOLLICLE		3

D TRANS B	# EX	6
INFLAMMATION, ACUTE, DERMIS		5
INFLAMMATION, SUBACUTE, DERMIS		6
INFLAMMATION, HAIR FOLLICLE		4

D TRANS C	# EX	6
INFLAMMATION, ACUTE, DERMIS		5
INFLAMMATION, SUBACUTE, DERMIS		6
INFLAMMATION, HAIR FOLLICLE		4
INFLAMMATION, PANNICULUS		1

NAIVE	# EX	6
INFLAMMATION, ACUTE, DERMIS		4
INFLAMMATION, SUBACUTE, DERMIS		6
INFLAMMATION, HAIR FOLLICLE		4

There were, however, two major treatment related effects as noted from the report prepared by the histopathologists. First the neutrophil infiltrates were present in superficial dermis of all D-TRANS treated skin sites (except animal # 32 where the skin samples were not collected). This indicates acute inflammation of dermis unlike the skin sample from the naïve sites (where no D-TRANS system was applied). Secondly in animal #14 severity of such inflammation was increased. In addition, in this animal inflammation of the panniculus (adipose tissue) was also noted. This finding was characterized by infiltration of macrophages, lymphocytes, and neutrophils in the panniculus. The Applicant does not consider it as treatment related because there were no inflammatory changes in the tissue between panniculus and superficial dermis. The applicant believed that this change might be due to the minor trauma that is pressure related to the adhesive. The reviewer observed that the animal #14 weighed the most 829 g (Applicant's table 1 with individual body weight reproduced as follows) compared, so adipose tissue might be more available to this animal which might also be a reason for

inflammation of panniculus this animal indicating that the injury associated with the D-TRANS system might associate with individual body mass.

TABLE 1: Individual Body Weights

(Page 1 of 1)

n=6

Guinea Pig Number	Sex	Day 0 (g)	Day 6 (g)	Change in BW [†] , %
06	F	670	631	-5.8
14	F	829	763	-8.0
32	F	713	692	-2.9
42	F	816	765	-6.2
74	F	730	689	-5.6
84	F	743	710	-4.4
Mean:		750.2	708.3	-5.48
Standard Deviation:		61.3	50.6	1.72

[†] % change in body weight = (final weight – initial body weight/initial weight)(100)

Study title: A Primary Skin Irritation Study of D-TRANS[®] Fentanyl systems in Hairless Guinea Pigs

Key study findings:

- The purpose of this study was to evaluate the safety of the 1 cm² D-TRANS system (transdermal patch) which contains fentanyl (approximately 0.4 mg/patch)
- To evaluate the safety six hairless guinea-pigs were applied with the patches topically on the intact dorsal skin for 96 hours and the primary irritation index was assessed for 48 hrs post patch removal.
- The data appear to show no fentanyl related increase in skin irritation.
- The residual drug analyses from the patch showed that 0.13 mg fentanyl was released over the 96 hr application period which is equivalent to 1.35 µg/cm².hr

Study no.: TR-03-5716-001

Volume # and page #: Module 2 eCTD submission; pages 1-50

Conducting laboratory and location: ALZA Corp.; Mountain View, CA

Date of study initiation: April 4, 2003

GLP compliance: Yes

QA reports: Yes

Drug, vehicle, lot #, and purity:

Drug: 1 cm² D-TRANS[®] (w/fentanyl);

The D-TRANS fentanyl article is composed of a backing layer, (b) (4) with fentanyl and a protective liner which is to be removed prior to application (refer to the Applicant's schematic diagram).



The ALZA code and control #s for the ingredients is reproduced as follows in the Applicant's Fig 1.

FIGURE 1: Formulation and Schematic Diagram

Formulation		
Components	Materials	ALZA Code/Control Number

Methods

Doses: The fentanyl content in the 1 cm² D-TRANS system was approximately (b) (4) mg. The Applicant's study scheme is reproduced in fig 2.

FIGURE 2: Study Schema

Study Day	Date	Task
0	4/4/03	Guinea pig BW/CO; test article application, bandage/animal check
1	4/5/03	Bandage/animal check
2	4/6/03	Bandage/animal check
3	4/7/03	Bandage/animal check
4	4/8/03	Test article removal, 30-40 min post-removal scoring
5	4/9/03	24-hour post-removal scoring
6	4/10/03	48-hour post-removal scoring; guinea pig BW/CO; guinea pig euthanasia

Note: BW/CO = body weights and clinical observations

Study design: Six female hairless guinea-pigs (strain Ibm: GO-HI hr) were used in this study. Each of the six guinea pigs had one 1 cm² D-TRANS[®] fentanyl articles applied topically on intact dorsal skin for approximately 96 hours. The site of application was cleaned with alcohol and dried prior to the application of the D-TRANS system. The dosing plan is reproduced as follows from the Applicant's study design.

**FIGURE 3: Dosing Plan
(Page 1 of 1)**HEAD

I II

1 cm² D-TRANS[®] fentanyl test article

Guinea Pig (1) <u>HEAD</u> I	Guinea Pig (2) <u>HEAD</u> II	Guinea Pig (3) <u>HEAD</u> I
Guinea Pig (4) <u>HEAD</u> II	Guinea Pig (5) <u>HEAD</u> I	Guinea Pig (6) <u>HEAD</u> II

After the 96 hrs of application, the sites were scored for erythema, eschar, and edema at 30-40 min, 24 hrs, and 48 hrs following Draize's method. Primary irritation index (PII) was calculated for each formulation. The treated skin tissues were subjected to histological evaluation.

The sites were scored for erythema, eschar, and edema at 30-40 min, 24 hrs, and 48 hrs following Draize's method and the primary irritation index (PII) was calculated for each formulation. The Draize method and PII is described previously with the review of toxicity study report # TR-02-5715-035.

Results: The summary of the data from the PII analyses is reproduced as follows from the Applicant's table # 2. Note that animal #s 3, 4 and 6 had erythema at 30 mins post removal of the D-TRANS patch, however, at 48 hrs no erythema was noted, therefore, the test article related irritation if any has been recovered shortly. Also, the Applicant noted that animal # 4 had abrasion in the neck area, this animal had erythema for a longer duration (at least 24 hrs) compared to the other animals.

TABLE 2: Skin Irritation Data
1 cm² D-TRANS[®] fentanyl

Score Time		Guinea Pig Number (Application Site)					
		01*(I)	02(II)	03(I)	04(II)	05(I)	06(II)
0.5 Hour	Erythema						
	Edema						
	Total, Erythema+Edema						
24 Hour	Erythema						
	Edema						
	Total, Erythema+Edema						
48 Hour	Erythema/Edema						
	Total, Erythema+Edema						

*No article on animal at time of article removal.

$$\text{Primary Irritation Index} = \frac{\text{Sum of scores at 0.5 hour and 48 hour}}{\text{Number of observations}} = \frac{3}{12} = 0.3$$

The Applicant evaluated the residual drug (fentanyl and naltrexone) not by analyzing fentanyl from the intact and worn D-TRANS matrix but by estimating the drug release from 1 cm² system by analyzing 42 cm² fentanyl article as shown in the Applicant's table 3. Note that an average of approximately 0.13 mg of fentanyl was released over the 96 hr time period which is equivalent to 1.35 cm².hr.

TABLE 3: Analytical Testing Results

	Analytical Request no.	Fentanyl Content, mg/1cm ² system
Before in-Life ^a (n=10)	<u>D-TRANS[®] fentanyl</u> 49855	0.4231
		0.4271
		0.4257
		0.4288
		0.4260
		0.4269
		0.4286
		0.4269
		0.4283
		0.4269
		Mean
		SD
After in-Life ^a (n=5)	SS3870	0.4226
		0.4250
		0.4257
		0.4231
		0.4248
		Mean
Worn Articles ^b (n=5)	48293	SD
		0.2937
Estimated Drug Released ^c	0.4260-0.2937 ^c	0.1323

^a Analyses performed on 42 cm² articles; values reported here have been adjusted to reflect 1 cm² article.

^b Analysis was performed on 5 pooled articles; value reported here is mg/1 article.

^c Estimated drug released = unused articles drug content (mean of before in-life and after in- life) – mean worn article drug content.

Study title: Subchronic Skin Irritation Study using D-TRANS[®] (Fentanyl) systems with Naltrexone HCl/EVA-28 in Hairless Guinea Pigs

Key study findings:

- Hairless guinea pigs (6/sex/group) received 9 topical applications of the respective test and control article to the dorsal skin area over 27 days, (one application every 72 hrs).
- The test and the control articles are D-TRANS system (which contains (b) (4) a novel excipient) wo/naltrexone wo/fentanyl, D-TRANS w/naltrexone wo/fentanyl, and D-TRANS w/naltrexone, w/fentanyl.
- The Applicant analyzed the residual drug content from the patch, clinical observation, body weights, cumulative irritation index, and histology of the skins.
- The residual drug analyses revealed that the skin flux of fentanyl after the application of the first patch in 3.47 µg/cm².hr and 2.5 µg/cm².hr suggesting a change in the absorption of fentanyl over a period of 27 days in the guinea pigs.

- The clinical observation noted scratching in all animals irrespective of the treatment group. The cumulative irritation index did not show any differences in the irritation index between the D-TRANS system wo/fentanyl wo/naltrexone and the D-TRANS system w/fentanyl w/naltrexone. Erythema was observed in most of the animals over the 27 day of the treatment period. The incidence of erythema was observed to be higher in females than in males. However, after the 48 hrs of the recovery period the incidence of erythema was reduced indicating recovery.
- The histological lesion of the skin indicated minimal to moderate acanthosis, hyperkeratosis, inflammation of hair follicles, and sub acute inflammation in all animals indicating that the D-TRANS system might have initiated this skin lesions.
- The naive areas of the skin where the patches were not applied also showed similar findings which led Applicant to suggest that these effect are non specific, however, the result might also suggest that the effect of the D-TRANS might not be restricted to the areas of application. The skins of the animals without any patch were not examined. Therefore the cause of such findings could not be appropriately analyzed.
- In addition to the above mentioned findings, parakeratosis were noted in 3/6 females in which D-TRANS w/fentanyl w/naltrexone were applied. No such findings were noted in males from the same group or in the animals treated with D-TRANS wo/fentanyl wo/naltrexone. The findings suggests that the parakeratosis might be a drug induced effect, the biological significance of such findings are not yet known.

Study no.: TR-02-5715-037

Volume # and page #: Module 2 eCTD submission; pages 1-100

Conducting laboratory and location: ALZA Corp.; Mountain View, CA

Date of study initiation: October 28, 2002

GLP compliance: Yes

QA reports: Yes

Drug, vehicle, lot #, and purity:

Following products were tested in the current study:

Drug: 1.25 cm² D-TRANS® (w/fentanyl, w/naltrexone);

Vehicle: 1.25 cm² D-TRANS® (wo/fentanyl, wo/naltrexone);

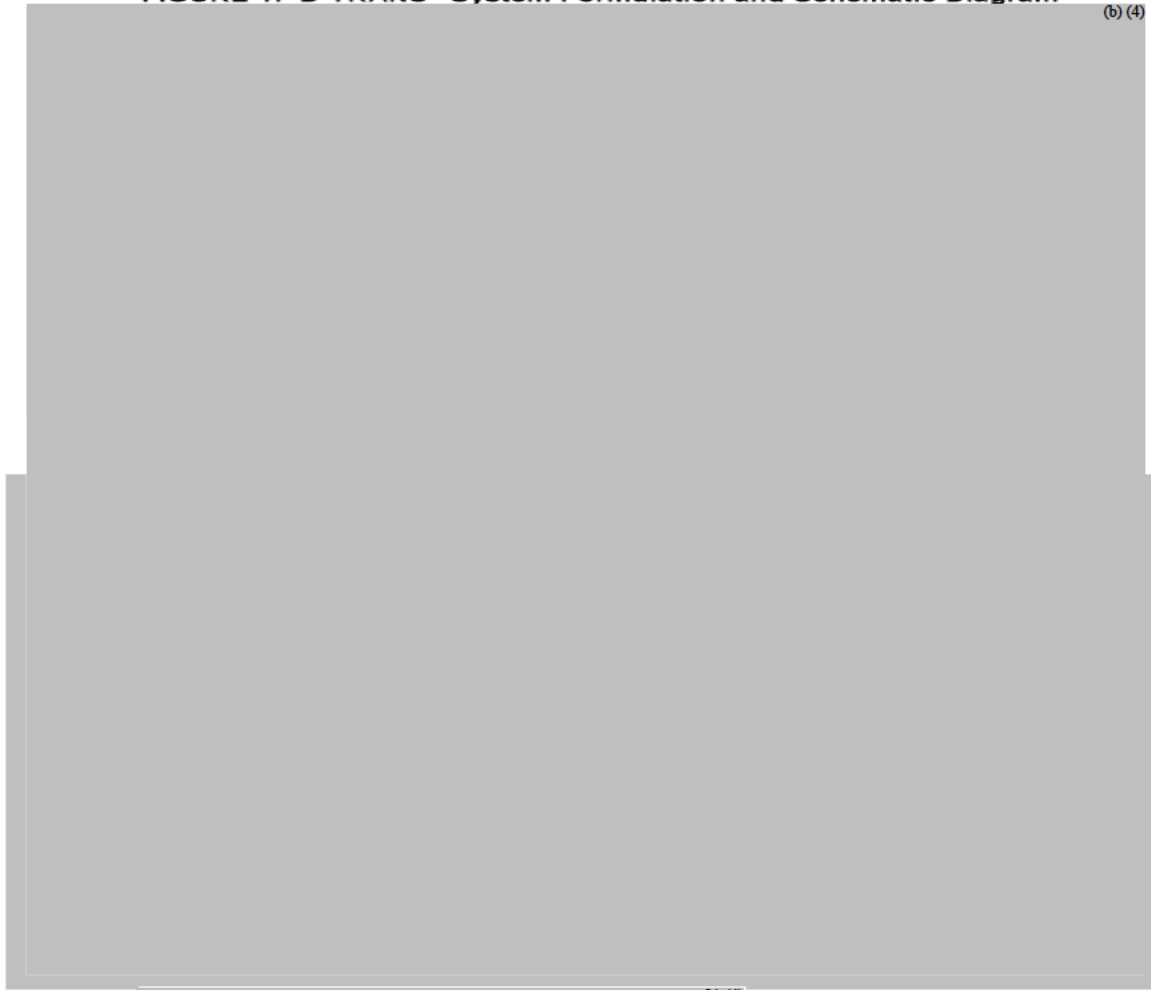
Control: 1.25 cm² D-TRANS® (wo/fentanyl, w/naltrexone);

D-TRANS[®] System is composed of a drug reservoir (b) (4) adhesive with or without fentanyl, a (b) (4), an (b) (4) layer (with or without naltrexone HCl) and a (b) (4) backing layer. Purity information was not provided. The Applicant did not provide the lot #s for any of the ingredients, however, ALZA's code and control #s are provided with the formulation in the Applicant's table.

Formulation and schematics are reproduced from the Applicant's submission as follows.

FIGURE 1: D-TRANS[®] System Formulation and Schematic Diagram

(b) (4)



Note that (b) (4) **which is a novel excipient.**

Methods

Doses:

Fentanyl and naltrexone content of each formulation are reproduced from the Applicant's table A as follows.

Table A: Test and Control Systems

D-TRANS [®] system (1.25 cm ²) ^a	Target Content	
	Fentanyl Base	Naltrexone Base
D-TRANS [®] (w/o fentanyl, w/o naltrexone), NB# 7223:39-40; 7011:99-100	0 mg	0 mg
D-TRANS [®] (w/o fentanyl, w/ naltrexone HCl/EVA-28), NB# 7223:39-40, 43; 7011: 102, 109	0 mg	1.88 mg
D-TRANS [®] (w/ fentanyl, w/ naltrexone HCl/EVA-28), NB# 7223:39-40, 44-46; 7011:102, 109	0.50 mg	1.88 mg

^a Received as 2.5 cm² systems

The D-TRANS[®] (fentanyl) systems with naltrexone HCl were received as 2.5 cm² systems and were targeted to contain 1mg of fentanyl and 3.76 mg naltrexone per system. However, for the current study each of the D-TRANS system was cut into half to while on system line, thereby yielding approximately 1.25cm² systems.

Study design: Both male and female hairless guinea-pigs (strain IAF: HA-HO-hr) were used in this study. Guinea pigs were divided into the following three groups as shown in the following table reproduced from the Applicant:

Group	n	Treatment
1	5M/5F	D-TRANS [®] system (w/o fentanyl, w/o naltrexone)
2	6M/4F	D-TRANS [®] system (w/o fentanyl, w/ naltrexone HCl)
3	5M/5F	D-TRANS [®] system (w/ fentanyl, w/ naltrexone HCl)

M = male; F = female

n* note that Group 2 has 4F and 6M; this is because one of the females developed skin rashes prior to the treatment and the Applicant replaced that with a male since no females were available.

Each animal got 9 topical applications to dorsal skin and each application was worn for approximately 72 hrs. Thus the study lasted for 27 days. Prior to each application the administration sites were cleaned with isopropyl alcohol and dried. The D-TRANS systems were secured by bandaging by the Micropore[®] and Vetrap[®]. The application was rotated between three different sites in each animal. The dosing plan is reproduced as follows from the Applicant's study design.

FIGURE 3: Dosing Plan

(Page 1 of 1)

Site locations on backs of hairless guinea pigs
HEAD

I II
 III

Site	Application No.
I	1, 4, 7
II	2, 5, 8
III	3, 6, 9

The Applicant evaluated the residual drug (fentanyl and naltrexone) by analyzing fentanyl and naltrexone from the intact and worn D-TRANS matrix. The body weights and the clinical observations were monitored, prior to the application of the test article and on study Days 0, 6, 12, 18, 24. The application sites were scored for erythema, eschar, and edema at 30-40 min, 24 hrs, and 48 hrs following Draize's method and the irritation potential was analyzed according to the scale adopted from Parvo et al 1996 as reported in the review of the study # TR-02-5715-035. The animals were euthanized after the 48 hrs of observation period following the last application of the test articles and the treated skin tissues were subjected to histological evaluation.

Results:

The active ingredients fentanyl and naltrexone were analyzed from the D-TRANS patches from the unused system and the patches worn for 3 days (application # 1 and application # 9) for determining the residual drug content of the D-TRANS system. The reviewer noted from the Applicant's table#1 illustrating the stability and the residual drug analyses that the quantity of the fentanyl and naltrexone in the unused patch from the pre dosing time to the end of the study time was similar indicating that the fentanyl and the naltrexone content of the drug contained in the patches did not leached or lost by any other circumstances like interaction with the delivery system etc. The residual fentanyl analyses of application # 1 indicated that 0.25 mg of the drug has been absorbed over the 72 hrs of the application period; similarly the residual fentanyl analyses of application # 9 indicated that 0.31 mg of the fentanyl remained in the patch. This suggest that the absorption rate of the fentanyl might be higher (0.24/72hrs) in the first 3 days of the experiment compared to that of the last 3 days of the experiment (0.18/72 hrs). This is equal to a skin flux of 3.47 $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$ and 2.5 $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$ with the applications #1 and #9 respectively, suggesting that there might be a saturation in the absorption of the fentanyl with the repeated application of the D-TRANS patch.

TABLE 3: Summary of Stability and Residual Drug Analyses

System Type	n=10 ^a		D-TRANS [®] (w/o fentanyl, w/o naltrexone) Drug Content, (mg)		D-TRANS [®] (w/o fentanyl, w/ naltrexone HCl) Drug Content, (mg)		D-TRANS [®] (w/ fentanyl, w/ naltrexone HCl) Drug Content, (mg)	
			Fentanyl	Naltrexone	Fentanyl	Naltrexone	Fentanyl	Naltrexone
Unused, Drug Content ^b , Predose	Mean		0.0	0.0	0.0	1.29	0.49	1.96
	±SD		0.0	0.0	0.0	0.19	0.01	0.25
Unused, Drug Content ^c , End of Life	Mean		0.0	0.0	0.0	1.37	0.49	1.90
	±SD		0.0	0.0	0.0	0.08	0.00	0.13
Unused Systems ^d	Mean		0.0	0.0	0.0	1.33	0.49	1.93
	±SD		0.0	0.0	0.0	0.14	0.01	0.19
Residual, Application no. 1 ^e	Mean		0.0	0.0	0.0	1.07	0.25	2.10
	±SD		0.0	0.0	0.0	0.25	0.03	0.12
Residual, Application no. 9 ^f	Mean		0.0	0.0	0.0	1.10	0.31	2.02
	±SD		0.0	0.0	0.0	0.22	0.05	0.22
Residual Drug ^g	Mean		0.0	0.0	0.0	1.08	0.28	2.06
	±SD		0.0	0.0	0.0	0.23	0.05	0.17
Estimated Drug Released ^h	Mean		0.0	0.0	0.0	0.25	0.21	-0.13

^a D-TRANS[®] (w/o fentanyl, w/naltrexoneHCl/EVA-28) group had n=6 systems at Application no. 9;

D-TRANS[®] (w/ fentanyl, w/naltrexone HCl/EVA-28) group had n=9 systems at Application no. 9

^b Data from AR nos. 48282, 48283, 48284; values reported here have been adjusted to reflect 1.25 cm² system

^c Data from AR nos. 48295, 48296, 48297; values reported here have been adjusted to reflect 1.25 cm² system

^d Mean of predose and end-of life

^e Data from AR nos. 49472, 49473

^f Data from AR nos. 49477, 49478

^g Mean of Individual data from Application nos. 1 and 9

^h Estimated Drug Released = Unused System Drug Content (mean of predose and end of life) – Mean Residual Drug Content

The in life observation from the study showed one mortality; one animal with D-TRANS w/naltrexone wo/fentanyl was found dead in the cage. The cause of death was not determined, no signs of injury were visible.

The cage side clinical observation noted scratch mark in 1/10, 1/1/10, and 3/10 animals from the vehicle (D-TRANS wo/naltrexone, wo/fentanyl), control (D-TRANS wo/fentanyl, w/ naltrexone), and the treatment group (D-TRANS w/fentanyl, w/naltrexone). The Applicant did not measure the severity of the findings. Because of the higher incidence of the findings in the treatment group compared to those of the controls, the findings are considered treatment related by the reviewer. Scratches were also observed in the heads and necks of animals from all three treatment groups; however, healing was visible within 24 hours after new system application. This finding might elucidate the fact that the vehicle control itself is irritable to animals but tolerated in general by the animals.

The cumulative irritation data are depicted as follows from the Applicant's table # 2 (page1-3). As shown in the table # 2-page 1 and table #2- page 3, there are no major

differences in the cumulative irritation index between the D-TRANS vehicle and the D-TRANS containing the active ingredients. Interestingly, the animals which received the D-TRANS application only did show greater incidence of erythema compared to those of the animals which received D-TRANS with the active ingredients. Also, in the vehicle control group edema was observed, no such findings were observed in the animals which received the patch containing the active ingredient. These findings indicate that the D-TRANS patch itself might be irritating to the hairless guinea pigs; in the absence of the appropriate control the degree of the irritation could not be estimated. Although not relevant for the current product, it is noted that the animals which received the patch containing naltrexone had the highest incidences of erythema and edema.

There was only one incidence of erythema with D-TRANS and the D-TRANS with fentanyl after 48 hrs of the withdrawal of the patches (table 2 page 3). This suggests that the irritation potential of the D-TRANS system is reversible.

TABLE 2: Summary of Skin Irritation Data

(Page 1 of 3)

Group 1: D-TRANS® (w/o fentanyl, w/o naltrexone)

Guinea Pig No. (Sex)	Application No. And Scoring Interval																					
	1 0.5 hr ery ed		2 0.5 hr ery ed		3 0.5 hr ery ed		4 0.5 hr ery ed		5 0.5 hr ery ed		6 0.5 hr ery ed		7 0.5 hr ery ed		8 0.5 hr ery ed		9 0.5 hr ery ed		9 24 hr ery ed		9 48 hr ery ed	
67S (M)	2	0	2	0	2	0	1	1	1	0	2	0	2	0	2	0	1	0	0	0	0	0
78S (M)	1	0	1	0	1	0	0	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0
79S (M)	2	0	2	0	1	0	1	0	1	0	1	0	2	0	1	0	1	0	0	0	0	0
80S (M)	2	0	0	0	2	0	1	0	1	0	1	1	2	1	1	0	1	0	0	0	0	0
858S (M)	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
12S (F)	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
13S (F)	1	0	2	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	0	0
31S (F)	0	0	0	0	2	0	1	0	1	0	1	0	1 ^a	0	0	0	1	0	1	0	0	0
41S (F)	0	0	1	0	1	0	1	1	0	1	0	0	1	0	0	0	2	0	1	0	0	0
52S (F)	0	0	0	0	1	0	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
Total	9		9		12		9		9		10		12		7		9		4		1	
Grand Total	89																					
CII	0.8																					

ery = erythema; ed = edema; hr = hours; M = male; F = female

CII – Cumulative Irritation Index = sum of erythema and edema/no. of observations per scoring interval

a - Scratch on site. Scratch not scored.

TABLE 2: Summary of Skin Irritation Data
(Page 2 of 3)
Group 2: D-TRANS^a (w/o fentanyl, w/ naltrexone HCl)

Guinea Piq No. (Sex)	Application No. And Scoring Interval																	
	1		2		3		4		5		6		7		8		9	
	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed
65S (M)	1	0	1	0	2	0	1	0	1	0	1	0	2	0	1	0	0	0
70S (M)	2	0	0	0	1	0	0	0	1	1	2	0	N/A – Animal found dead 11/18/02					
72S (M)	1	0	0	0	1	0	0	0	1	0	2	0	2	0	2	0	2	0
73S (M)	2	0	0	0	1	0	1	0	1	1	1	0	1	0	1	1	0	0
76S (M)	1	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	0
643S (M)	1	0	1	0	2	0	2	0	1	0	1	0	2 ^a	0	1 ^a	0	2	0
20S (F)	0	0	1	0	2	0	0	0	1	0	1	0	2	0	1	1	1	0
36S (F)	1	0	2	0	2	0	1	0	2	0	1	0	2	0	1	0	0	0
42S (F)	2	0	0	0	2	0	2	0	0	0	0	0	1	0	0	0	0	0
43S (F)	0	0	1	0	1	0	1	0	0	0	1	0	2	0	1	0	2	0
Total	11		8		16		10		12		12		16		12		8	
Grand Total	108																	
CII	1.0																	

ery = erythema; ed = edema; hr = hours; M = male; F = female

CII – Cumulative Irritation Index = sum of erythema and edema/no. of observations per scoring interval

a - Scratch on site. Scratch not scored.

TABLE 2: Summary of Skin Irritation Data
(Page 3 of 3)
Group 3: D-TRANS^a (w/ fentanyl, w/ naltrexone HCl)

Guinea Piq No. (Sex)	Application No. And Scoring Interval																	
	1		2		3		4		5		6		7		8		9	
	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed	0.5 hr ery	0.5 hr ed
68S (M)	2	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
69S (M)	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	2	0
71S (M)	0	0	1	0	2	1	0	0	0	0	1	0	0	0	0	0	0	0
74S (M)	1	0	0	0	1	0	1	0	0	0	1	0	1 ^a	0	0	0	2	0
77S (M)	2	0	1	0	2	0	1	0	2	0	2	0	2	0	1 ^a	0	0	0
3S (F)	0	0	1	0	2	0	1	0	1	1	0	0	0	0	1	0	2	0
14S (F)	1	0	1	0	1	0	0	0	1	0	1	0	2	0	2	0	0	0
18S (F)	1	0	1	0	0	0	1	0	0	0	1	0	2	0	1	0	1	0
35S (F)	1	0	0	0	1	0	1	0	1	0	1 ^a	0	1	0	1	0	0	0
59S (F)	0	0	1	0	1	0	1	0	1	0	0	0	0	0	1	0	1	0
Total	8		8		12		7		8		9		9		9		9	
Grand Total	83																	
CII	0.8																	

ery = erythema; ed = edema; hr = hours; M = male; F = female

CII – Cumulative Irritation Index = sum of erythema and edema/no. of observations per scoring interval

a - Scratch on site. Scratch not scored.

The histological lesions were evaluated by (b) (4)
the followings are the report codes for the analyses of the histology findings.

Reports Code and Abbreviations Table

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
U	Tissues unavailable/unsuitable for evaluation
S	Tissues not applicable to animal
*	Tissues not examined/not required by protocol
1	minimal
2	mild
3	moderate
4	marked
()	focal
[]	diffuse
<>	multifocal
P	Present
I	Bilateral
L	Unilateral
-	Diagnosis Not Applicable to Animal/Tissue
# EX	Number Examined
TR037	TR-02-5715-037
UNTREATED	Naive
GPIGS	Guinea Pigs
D-TRANS	D-TRANS®

Study ID: D-TRANS WITH NALTREX - Subchronic Skin Irritation Study
Using D-TRANS® (Fentanyl) Systems in Hairless Guinea Pigs

The histopathology table reproduced from Applicant indicated that the males treated with D-TRANS patch and D-TRANS patch with fentanyl and with naltrexone showed similar degree of acanthosis, hyperkeratosis, sub acute inflammation of dermis and hair follicles. The degree of severity for all of the above findings varied from minimal (1) to moderate (3). All of the inflammation findings are observed to be multi focal (<>) as designated by the Applicant CRO.

(b) (4)

SUBCHRONIC SKIN IRRITATION STUDY USING D-TRANS (FENTANYL) SYSTEMS
WITH NALTREXONE HCl/EVA-28 IN HAIRLESS GUINEA PIGS
ALZA CORPORATION STUDY NUMBER: TR-02-5715-037

TABULATED ANIMAL DATA

STUDY ID : D-TRANS WITH NALTREX		STUDY NUMBER: TR037			
FATE: ALL		GROUP: 1: D-TRANS system (w/o fentanyl, w/o naltrexone)			
DAYS ON TEST: ALL		SEX: MALE			
ANIMAL ID:	658S	67S	78S	79S	80S
SITE I	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	2	2	1	2
HYPERKERATOSIS, EPIDERMIS	2	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<1>	<1>	<1>
SITE II	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	1	2	1	1
HYPERKERATOSIS, EPIDERMIS	3	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	2	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<3>	<1>	<1>
SITE III	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	1	2	1	2
HYPERKERATOSIS, EPIDERMIS	2	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<3>	<1>	<2>
NAIVE	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	1	2	1	2
HYPERKERATOSIS, EPIDERMIS	2	3	2	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<2>	<1>	<1>

(b) (4)

SUBCHRONIC SKIN IRRITATION STUDY USING D-TRANS (FENTANYL) SYSTEMS
WITH NALTREXONE HCl/EVA-28 IN HAIRLESS GUINEA PIGS
ALZA CORPORATION STUDY NUMBER: TR-02-5715-037

TABULATED ANIMAL DATA

STUDY ID : D-TRANS WITH NALTREX		STUDY NUMBER: TR037			
FATE: ALL		GROUP: 3: D-TRANS system (w/ fentanyl, w/ naltrexone)			
DAYS ON TEST: ALL		SEX: MALE			
ANIMAL ID:	68S	69S	71S	74S	77S
SITE I	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	1	2	3	2	2
HYPERKERATOSIS, EPIDERMIS	2	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	2	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<3>	<2>	<1>
SITE II	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	1	1	3	1	1
HYPERKERATOSIS, EPIDERMIS	2	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	2	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<1>	<3>	<1>	<1>
SITE III	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	1	2	1	1
HYPERKERATOSIS, EPIDERMIS	2	2	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<1>	<2>	<3>	<1>	<1>
NAIVE	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	2	3	1	1
HYPERKERATOSIS, EPIDERMIS	3	3	3	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	2	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS	<2>	<2>	<3>	<1>	<1>

The histopathological analyses of the treated and naive skin sites from females are reproduced as follows. The result indicated that acanthosis, hyperkeratosis, sub acute inflammation and inflammation of the hair follicles were present. The degree of severity of such findings were similar to males that is minimal (1) to moderate (3) and there were no differences between the animals treated with D-TRANS and the animals treated with DTRANS w/fentanyl w/naltrexone in the incidence and severity of the above mentioned findings. However, parakeratosis were noted in 3 females treated with D-TRANS w/fentanyl and w/naltrexone. The parakeratosis were focal approximately 100 microns in diameters with 2-3 cell layer thickness. No such changes were noted in the animals treated with D-TRANS wo/fentanyl wo/naltrexone. Therefore the findings are considered related to the active ingredient by the reviewer. The Applicant believes that it might be due to a localized inflammatory response because in one animal this incidence was associated with neutrophils. One male (no female) with D-TRANS w/naltrexone and wo/fentanyl had parakeratosis of higher severity index than these females (D-TRANS w/fentanyl, w/naltrexone). Therefore the Applicant said that the possibility of the naltrexone involvement in the parakeratosis could not be ruled out. According to the reviewer, D-TRANS system itself might be responsible for the lesions like acanthosis,

hyperkeratosis etc. Fentanyl and naltrexone enhanced the incidence of parakeratosis in females, the biological relevance of the findings is not known.

(b) (4)

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**SUBCHRONIC SKIN IRRITATION STUDY USING D-TRANS (FENTANYL) SYSTEMS
WITH NALTREXONE HCl/EVA-28 IN HAIRLESS GUINEA PIGS
ALZA CORPORATION STUDY NUMBER: TR-02-5715-037**

TABULATED ANIMAL DATA

STUDY ID : D-TRANS WITH NALTREX		STUDY NUMBER: TR037			
FATE: ALL		GROUP: 1: D-TRANS system (w/o fentanyl, w/o naltrexone)			
DAYS ON TEST: ALL		SEX: FEMALE			
ANIMAL ID:	12S	13S	31S	41S	52S
SITE I	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	3	2	2	2	3
HYPERKERATOSIS, EPIDERMIS	3	2	2	2	2
INFLAMMATION, SUBACUTE, DERMIS	2	1	2	1	2
INFLAMMATION, HAIR FOLLICLE, DERMIS	<3>	<2>	<2>	<1>	<1>
SITE II	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	3	1	1	2	2
HYPERKERATOSIS, EPIDERMIS	3	2	2	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	2	2
INFLAMMATION, HAIR FOLLICLE, DERMIS	<3>	<1>	<1>	<2>	<1>
SITE III	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	2	1	2	1	2
HYPERKERATOSIS, EPIDERMIS	2	2	2	2	2
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	2	2
INFLAMMATION, HAIR FOLLICLE, DERMIS	<3>	<2>	<2>	<2>	<1>
MAIVE	-	-	-	-	-
ACANTHOSIS, EPIDERMIS	3	1	1	1	2
HYPERKERATOSIS, EPIDERMIS	2	2	2	2	3
INFLAMMATION, SUBACUTE, DERMIS	1	1	1	1	2
INFLAMMATION, HAIR FOLLICLE, DERMIS	<3>	<1>	<1>	<1>	<1>

(b) (4)

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**SUBCHRONIC SKIN IRRITATION STUDY USING D-TRANS (FENTANYL) SYSTEMS
WITH NALTREXONE HCl/EVA-28 IN HAIRLESS GUINEA PIGS
ALZA CORPORATION STUDY NUMBER: TR-02-5715-037**

TABULATED ANIMAL DATA

STUDY ID : D-TRANS WITH NALTREX		STUDY NUMBER: TR037				
FATE: ALL		GROUP: 3: D-TRANS system (w/ fentanyl, w/ naltrexone)				
DAYS ON TEST: ALL		SEX: FEMALE				
ANIMAL ID:		3S	14S	18S	35S	59S
SITE I		-	-	-	-	-
ACANTHOSIS, EPIDERMIS		2	2	1	2	2
HYPERKERATOSIS, EPIDERMIS		2	3	2	3	3
PARAKERATOSIS, EPIDERMIS		-	<1>	-	<1>	-
INFLAMMATION, SUBACUTE, DERMIS		1	2	2	2	1
INFLAMMATION, HAIR FOLLICLE, DERMIS		<2>	<2>	<3>	<1>	<2>
SITE II		-	-	-	-	-
ACANTHOSIS, EPIDERMIS		2	1	2	2	2
HYPERKERATOSIS, EPIDERMIS		2	2	2	2	2
INFLAMMATION, SUBACUTE, DERMIS		2	2	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS		<2>	<2>	<2>	<2>	<2>
SITE III		-	-	-	-	-
ACANTHOSIS, EPIDERMIS		2	2	2	2	2
HYPERKERATOSIS, EPIDERMIS		2	2	2	2	3
PARAKERATOSIS, EPIDERMIS		-	-	-	(2)	(1)
INFLAMMATION, SUBACUTE, DERMIS		1	2	2	2	1
INFLAMMATION, HAIR FOLLICLE, DERMIS		<2>	<2>	<2>	<2>	<2>
NAIVE		-	-	-	-	-
ACANTHOSIS, EPIDERMIS		2	1	2	2	2
HYPERKERATOSIS, EPIDERMIS		3	2	2	3	3
PARAKERATOSIS, EPIDERMIS		-	<1>	-	-	-
INFLAMMATION, SUBACUTE, DERMIS		1	1	1	1	1
INFLAMMATION, HAIR FOLLICLE, DERMIS		<1>	<2>	<2>	<1>	<1>

2.6.6.8 Special toxicology studies

Study title: Evaluation of the Sensitization Potential in Guinea Pigs of D-TRANS® Fentanyl systems with Naltrexone HCl

Key study findings:

- Female hairless guinea pigs, 10/group were used to assess the sensitization potential of the D-TRANS fentanyl system.
- The study consists of an induction period and one challenge period. The induction period was 21 days and consisted of nine applications with approximately 48 hrs/ application. Fourteen days after the application of the last induction the animals were challenged with the respective treatment. Each challenge treatments were worn for 48hrs, the application sites were scored at 2,

24, and 48 hrs. The positive control DNCB was worn for 24 hrs and the site was scored up to 72 hrs after the removal of the challenge article.

- Under this experimental condition D-TRANS fentanyl system appeared to be a non sensitizer. The transdermal patch system with or without the active ingredient, however, showed mild irritancy (primary and cumulative), indicating that the D-TRANS system is an irritant by itself.

Study no.: TR-02-5715-036

Volume # and page #: Module 2 eCTD submission; pages 1-89

Conducting laboratory and location: ALZA Corp.; Mountain View, CA

Date of study initiation: October 14, 2002

GLP compliance: Yes

QA reports: Yes

Drug, vehicle, lot #, and purity:

Following products were tested in the current study:

Drug: 2.5 cm² D-TRANS® (w/fentanyl, w/naltrexone);

Vehicle: 2.5 cm² D-TRANS® (wo/fentanyl, wo/naltrexone);

Control: 2.5 cm² D-TRANS® (wo/fentanyl, w/naltrexone);

Methods

Doses: 2.5 cm² D-TRANS® fentanyl system with naltrexone containing 1 mg fentanyl and 3.75 mg naltrexone as indicated in the following table from the Applicant.

Table A: Test and Control Systems

D-TRANS® system (2.5 cm ²)	Target Content	
	Fentanyl Base	Naltrexone Base
D-TRANS® w/o fentanyl w/o NTX	0 mg	0 mg
D-TRANS® w/o fentanyl with NTX	0 mg	3.75 mg
D-TRANS® fentanyl with NTX	1.0 mg	3.75 mg

Study design: The female hairless guinea pigs (IAF: HA-HO-hr), 10/group were used to assess the sensitization potential of the D-TRANS fentanyl system. Following treatment groups (table reproduced from the Applicant) were used.

Group	n	Induction Treatment	Challenge Treatment
1	10	D-TRANS [®] w/o fentanyl w/o NTX	D-TRANS [®] w/o fentanyl w/o NTX D-TRANS [®] fentanyl with NTX
2	10	D-TRANS [®] w/o fentanyl with NTX	D-TRANS [®] w/o fentanyl with NTX D-TRANS [®] w/o fentanyl w/o NTX
3	10	D-TRANS [®] fentanyl with NTX	D-TRANS [®] fentanyl with NTX D-TRANS [®] w/o fentanyl w/o NTX
4	5	0.05% (w/v) 1-chloro 2,4-dinitro-benzene (DNCB) in acetone (positive control)	0.05% (w/v) 1-chloro 2,4-dinitro-benzene (DNCB) in acetone (positive control) Acetone
5 ^a	5	Naïve control	

^a This group of animals was not dosed.

Note: w/o = without

The composition of the D-TRANS system is illustrated in the Applicants figure # 1 in the review of the study # TR-02-5715-035.

The study consists of an induction period and one challenge period. The induction period was 21 days and consisted of nine applications with approximately 48 hrs/ application. The patches were applied on the cleaned dorsal skins, the site of application were not rotated. For the positive control, however, the application site was moved to ventral site from the Application # 6 due to the presence of eschar in the dorsal skin. The skins were evaluated for irritation 2 hrs post removal of each application and 2 and 24 hrs post removal of the last application. The 0.05 % (w/v) 1-chloro-2, 4 dinitrobenzene (DNCB) in acetone DNCB was used as positive control; the control article was applied nine times, each application was worn for 24 hrs.

Fourteen days after the application of the last induction the animals were challenged with the respective treatment as indicated in the Applicant's study design table. Each challenge treatments were worn for 48hrs, the application sites were scored at 2, 24, and 48 hrs. The positive control was worn for 24 hrs and the site was scored up to 72 hrs after the removal of the challenge article.

Results:

The Applicant scored the primary and cumulative irritation index as indicated by the irritation score after the removal of the first and last application in the Applicant's table shown as follows. The irritation was scored according to the system developed by Draize et al described with the review of study # TR-02-5715-035. All of the D-TRANS systems with or without the active ingredient were observed to induce mild irritation. There was no evidence of cumulative irritation for the D-TRANS systems. The positive control showed a primary and cumulative irritation index of 1.6 and 5.6 respectively.

Irritation Indexes for the First and Ninth Applications

Group	n	Formulation	Irritation Index ^{a, b} (Irritation Category ^c)	
			First Induction	Ninth Induction
1	10	D-TRANS [®] w/o fentanyl w/o NTX	1.2 (mild)	1.1 (mild)
2	10	D-TRANS [®] w/o fentanyl with NTX	1.5 (mild)	1.1 (mild)
3	10	D-TRANS [®] fentanyl with NTX	1.2 (mild)	0.9 (mild)
4	5	0.05% (w/v) DNCB in acetone	1.6 (mild)	5.6 (severe)

^a Groups 1, 2, and 3 treatment sites were evaluated at 2-hours after first Induction removal and after 2- and 24-hours after the ninth Induction removal. Group 4 treatment sites were evaluated at 2- and 24-hours after removal of first and ninth Inductions.

^b Irritation Index = erythema + edema scores divided by the number of observations at timepoints indicated in footnote ^a.

^c Irritation Category:

0-0.5 = none to negligible

0.6-2.0 = mild

2.1-5.0 = moderate

5.1-8.0 = severe

The response for sensitization was characterized by a combination of erythema and edema and the results were considered positive if the combined score was >2 at 48 hrs post patch removal. As observed from the Applicant's Table E, reproduced as follows, no sensitization was observed following the challenge treatment.

Table E: Incidence of Positive Reactions

Induction Treatment	Challenge Treatment				
	D-TRANS [®] w/o fentanyl w/o NTX	D-TRANS [®] w/o fentanyl with NTX	D-TRANS [®] fentanyl with NTX	0.05% DNCB	Acetone
D-TRANS [®] w/o fentanyl w/o NTX	0/10 (0% = Weak)	N/A	0/10 (0% = Weak)	N/A	N/A
D-TRANS [®] w/o fentanyl with NTX	0/10 (0% = Weak)	0/10 (0% = Weak)	N/A	N/A	N/A
D-TRANS [®] fentanyl with NTX	0/10 (0% = Weak)	N/A	0/10 (0% = Weak)	N/A	N/A
0.05% DNCB	N/A	N/A	N/A	5/5 (100% = Extreme)	0/5 (0% = Weak)

Note: Incidence of positive reactions: 0-8% of positive responders = Weak
81-100% of positive responders = Extreme

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATION

Refer to the executive summary section.

References

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(b) (4)

(b) (4)

IARC (International Agency for Research on Cancer), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1995. Dry Cleaning, Some Chlorinated Solvents and other Industrial Chemicals 63.

(b) (4)

(b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

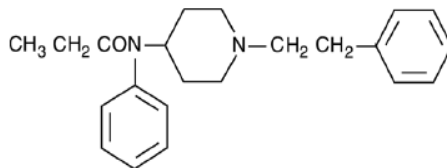
APPENDICES

APPENDIX 1: CARCINOGENICITY STUDY REVIEW (REVIEWED BY STEVE LESHIN, PH.D.).**2.6 PHARMACOLOGY/TOXICOLOGY REVIEW**

NDA number: 19-813, S044
Review number: 1
Sequence number/date/type of submission: 15-Dec-2008; SLR
26-Nov-2008; N 000
Information to sponsor: No
Sponsor and/or agent: Johnson and Johnson
Manufacturer for drug substance: (b) (4)

Reviewer name: L. Steven Leshin, Ph.D.
Division name: Division of Anesthesia, Analgesia, and
Rheumatology Products
HFD #: 170
Review completion date: July 18, 2008

Drug:
Trade name: Duragesic[®] CII (Fentanyl transdermal system)
Generic name: Fentanyl
Code name: None
Chemical name: N-Phenyl-N-(1-(2-phenylethyl)-4-piperidiny) propamide
CAS registry number:
Molecular formula/molecular weight: C₁₂H₂₈N₂O /336.5
Structure:



Studies reviewed within this submission:

(Study TR-02-5715-021) 104-Week Subcutaneous Injection Carcinogenicity Study with Fentanyl Hydrochloride in Rats

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Carcinogenicity summary

A two year carcinogenicity study in rats was conducted in rats. Subcutaneous administration of fentanyl HCl at daily single doses of 10, 33 or 100 µg/kg/day in females and at dose levels of 10 and 33 µg/kg/day in males did not result in an increased incidence of neoplastic lesions. Males in the 100 µg/kg/day dose group were sacrificed at week 36 due to a higher than expected incidence of mortality and also aggressiveness and were not included in the final carcinogenicity analysis, although they also had no increased incidence of tumors at the time of sacrifice.

Notable other findings included brain mineralization/necrosis that occurred in 12 of 65 males in the 100 µg/kg/day dose group. This change was graded minimal to slight in most, moderate in two and moderately severe in one of the affected males. Mineralization/necrosis was also present in the brain of three 100 µg/kg/day females and one 10 µg/kg/day female sacrificed at the study termination. Necrosis was also present in the cerebral cortex of one 100 µg/kg/day female. It is unclear as to whether this represents a primary effect of fentanyl or a secondary change possibly a response from hypoxia, since fentanyl is a respiratory depressant.

Corneal mineralization/epithelial degeneration occurred in the eyes with an increased incidence in males (6/65) and females (11/65) in the 100 µg/kg/day dose groups. These changes (graded as minimal to slight) occurred as a focal lesion in the center of the cornea and were characterized by mineralization of the subepithelial membrane associated with degeneration of the overlying corneal epithelium. This may be associated with persistent dry eye.

Giant cell pneumonia associated with foreign (plant, feed-like) material was a notable histopathologic change present with a very high incidence in the lungs. The finding was compatible with an aspiration of feed material, evident in alveoli histopathology.

Study title: 104-Week Subcutaneous Injection Carcinogenicity Study with Fentanyl Hydrochloride in Rats

Key study findings:

Once-daily subcutaneous administration of fentanyl HCl to Sprague Dawley Crl:CD CI(SD)IGS BR rats at dose levels of 10 and 33 µg/kg/day in males for up to 96 weeks

and at dose levels of 10, 33, and 100 µg/kg/day in females for up to 102 weeks did not result in an increased incidence of neoplastic lesions.

Adequacy of the carcinogenicity study and appropriateness of the test model: The study was adequately conducted and analyzed.

Evaluation of tumor findings: The tumor findings were evaluated and analyzed appropriately.

Study no.: TR-02-5715-021

Conducting laboratory and location: (b) (4)

Date of study initiation: March 3, 2003; in-life phase March 18, 2003 to March 4, 2005; study report issued 8/15/06; Sponsor study director approved 9/5/06

GLP compliance: yes

QA report: yes

Drug, lot #, and % purity:

Fentanyl hydrochloride, Lot 9901302, Purity 99.2%, weeks of use 1-58

Lot 0117793, Purity 99.4% weeks of use 59-76

Lot 0409503, Purity 98.5%, weeks of use 77-103

Control vehicle: 0.9% sterile saline

The "Test Article" was a solution of fentanyl hydrochloride in 0.9% sterile saline.

Concentration Verification Analysis of the dose formulations confirmed that all dose concentrations were within $\pm 5\%$ of the target concentrations, with two exceptions. The dose formulations used on the first day of week 38 and prepared for week 92 were lower than expected and new preparations were prepared. Uniformity, stability tests were confirmed in previous studies.

CAC concurrence: Yes, at the ECAC meeting Nov 26, 2002 an additional higher dose group was recommended, as summarized below.

The doses used on this study were recommended by the FDA following review of the results of a 3-month rat toxicity study (ALZA Study No. TR-01 5715-024), in which fentanyl HCl was administered subcutaneously at 10, 33, 100, and 200 µg/kg/day. The Sponsor proposed a maximum dose of 33 µg/kg/day. Based on the findings, the maximum tolerated dose for once daily subcutaneous administration of fentanyl HCl to rats for at least 13 weeks was defined as 100 µg/kg/day (dose expressed as free base).

- The Committee recommended doses of 0, 0, 0.01, 0.033 and 0.1 mg/kg/day.
- The sponsor is recommended to closely monitor the animals and should notify the Agency should excessive clinical signs be seen, such as self-mutilation.
- For the rat study, if the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

METHODS

Doses: 0, 0, 10, 33, 100 µg/kg/day fentanyl base

Basis of dose selection (MTD, MFD, AUC etc.): MTD

Species/strain: Rats, Crl:CD 1(SD)IGS BR

Number/sex/group (main study): 55/sex/dose, except for 65/sex/dose in the 100 µg/kg/day group

Route, formulation, volume: subcutaneous injection daily for up to 103 weeks at a dose volume of 2.5 mL/kg/day.

The Sponsor justification for subcutaneous administration to support the proposed human transdermal route is that this route offers flexible doses, ensures systemic exposure, and in many respects, mimics the trans-dermal route.

The reviewer concurs that this route is appropriate.

Frequency of dosing: once daily for 2 years

Satellite groups used for toxicokinetics or special groups:

Age: 7 weeks (males: 215-293 g; females: 132 to 197 g)

Animal housing: Rats of the same sex were housed two/cage during the acclimation period, after which they were individually housed and offered food and water ad libitum.

Restriction paradigm for dietary restriction studies: Neither food amounts nor dietary restriction were mentioned in the study.

Drug stability/homogeneity: Drug uniformity and stability were confirmed in previous studies; uniformity for concentrations of 4 and 148 µg/mL and stability for 4 and 5000 µg/mL after 8 days of 2-8°C refrigeration and 6 hours at room temperature.

Dual controls employed: Yes

Interim sacrifices: There were no scheduled interim sacrifices.

Deviations from original study protocol:

The Sponsor communicated with the Division, twice during the study, the first time was within a few months of starting the study with concerns about aggressiveness in high dose males, and the second time late in the study concerning earlier than anticipated mortalities.

November 2003: Alza contacted the Division requesting concurrence to sacrifice the male high dose fentanyl rats that were becoming so aggressive that the handlers were having trouble injecting them, were getting bit even though they were using chain mail gloves and were inadvertently injecting themselves.

Based upon feedback from Drs. Jacobson-Kram, Timothy McGovern and Jeri El-Hage (members of the original ECAC for this protocol), the Division contacted the sponsor on November 13, 2003 and indicated that the welfare of the animal handlers should be taken into consideration and therefore it was acceptable to sacrifice the high dose male animals (animals were at week 36 of the study). It

was noted in the Sponsor's email of Nov 2004, concerning animal survival, see below.

The Group 5 (100 µg/kg/day) males were terminated early during week 36 (day 246 or 247) and were not included in the carcinogenicity analysis.

November 4, 2004: Alza contacted the Division concerned by an apparent steady decrease in survival of animals in the study. At week 89, the number of surviving males in the mid-dose group was 27 (out of 55). The sponsor requested input regarding when they should consider discontinuing the study.

Following consultation with members of the eCAC, the Division, on Feb 1, 2005, recommended following:

- For the males, if any group drops to 20 animals, stop dosing that group only and continue the study. If, however, the number of remaining animals in any group drops to 15 prior to scheduled sacrifice, sacrifice all males and the tissues analyzed.
- For the females, if a group drops to 20 animals, stop dosing that group only. If any group drops to 15 remaining animals, it is acceptable to terminate all females for tissue analysis.
- For the rat study, if the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

Dosing of Group 3 males was terminated on day 641 (week 92). Terminal sacrifice for males was conducted during week 97 (days 674 and 675). Group 1, 2, and 4 males were dosed until the day prior to scheduled sacrifice. Dosing of Group 1 females was terminated on day 688 (week 99). Terminal sacrifice for females was conducted during week 103 (days 717 and 718). Group 2-5 females were dosed until the day prior to scheduled sacrifice.

Study design

Group	No. of Animals		Fentanyl Dose Level ^a (µg/kg/day)	Dose Volume (mL/kg/day)	Fentanyl HCl Concentration ^a (µg/mL)
	Male	Female			
1 (Control)	55	55	-	2.5	-
2 (Control)	55	55	-	2.5	-
3 (Low)	55	55	10	2.5	4.440
4 (Mid)	55	55	33	2.5	14.652
5 (High)	65	65	100	2.5	44.400

^a Dose levels are expressed as fentanyl base, whereas the concentrations are expressed as fentanyl HCl, using a salt/base ratio = 1.11/1.

Statistical Analysis of Survival and Neoplastic Lesions:

Evaluations of trend and heterogeneity of survival data were performed using the Cox- Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI) Life Table Package (Thomas, Breslow, and Gart, 1977).

Neoplastic lesions were chosen for statistical analyses if the incidence in at least one treated group was increased or decreased by at least two occurrences over the control group. The incidental tumors (ie, tumors that were not assigned to be the cause of death of the animals by the study pathologist) were analyzed by linear logistic regression of tumor prevalence (Dinse and Lagakos, 1983). The fatal and palpable (superficial) tumors were analyzed by the Cox-Tarone binary regression method using the death time or the first palpation time (as applicable) as a surrogate for the tumor onset time. Incidental tumors were analyzed by logistic regression of tumor prevalence tests.

In the case of any particular tumor type, where the study pathologist assigned the tumor in question as being the cause of death of a subset of the animals and the rest of the animals was assumed to be dead of other competing risks, IARC-type (Peto et al., 1980) cause of death analysis was performed. Specifically, the subset of the tumors which was assigned to be the cause of death by the study pathologist was analyzed by Cox-Tarone logistic regression under life table techniques. The subset, which was considered incidental by the pathologist, was analyzed by logistic regression of tumor prevalence. Tumor types in which cause of death was undetermined were treated as incidental for statistical purposes. The score statistics and their respective variances from the above tests were then used to compute the combined evidence as described by Gart, et al (1986). If there was only one tumor belonging to one of the two categories (fatal and incidental) in a test, they were combined with the other category for the purpose of statistical analyses. In addition, for incidental tumors only, in the cases where there was lack of convergence for the asymptotic test of the logistic regression method or when the tables were sparse (<5), the exact probability of significance was obtained by using LogXact-Turbo. (Cytel Software Corporation, 1993).

The Cox-Tarone method is more sensitive to late deaths and the Gehan-Breslow method is more sensitive to early deaths due to treatment. Week 105 was treated as the end of the study in the NCI package for the males and females, respectively. Those animals that were sacrificed at the scheduled interval and the animals that were sacrificed for other reasons (gavage-related or aggressive behavior) were censored in the analyses. Continuity-corrected one-sided tail probabilities for trend and group comparisons were evaluated at 5.0% significance level. Additionally, Kaplan-Meier product limit survival curves were presented for males and females separately.

The benign and malignant neoplastic incidences were evaluated both separately and combined, where appropriate. The criteria for combination were based on the

work of McConnell, et al. (1986). The incidences of multiple-organ and systemic neoplastic findings, such as hemangioma, lipoma, fibroma, fibrosarcoma, osteosarcoma, endometrial stromal polyp, and endometrial stromal sarcoma, were counted by animal, not by tissue. They were evaluated statistically if they met the selection criterion for the analysis.

Trend and one-sided control versus treated group comparisons were evaluated at the 5.0% significance level. One-sided tail probabilities for trend and group comparisons are shown in Text Tables 3 and 4 for males and females, respectively. Further, in the cases where the intermediate dose groups did not have a complete histopathology examination, they were excluded from statistical analyses and only control versus high-dose group comparisons were performed provided they both had complete histopathology performed in the study. Continuity correction was done for all asymptotic tests.

RESULTS

Mortality: checked twice daily (am and pm)

Two high-dose rats died during the first two weeks (1 male on day 4, and 1 female on day 9) of the study, and were replaced with rats in accordance to Covance standard operating procedures and those two rats were not included in the overall analysis.

The survival results over the 2-year study are presented in the table below, and the figures that follow the table.

Males: Survival of the 100 µg/kg/day males (Group 5) was relatively low (78% versus at least 95% in the other male groups) at week 35, although it should be noted that some animals were euthanized due to excessively aggressive behavior. This group was terminated during week 36 due to behavioral changes characteristic of animals in distress (unthrifty appearance, markedly thinner than those of the other dose groups, inordinately sensitive to touch, and unusually aggressive) as well as the relatively low survival rate. The 100 µg/kg/day male group excluded from all statistical analyses.

Due to decreased survival (36% survival; n=20), dosing of 10 µg/kg/day male group (Group 3) was terminated on Day 641 (week 92), and terminal sacrifice for all male groups was conducted during week 97.

The two male control groups showed statistically similar mortality rates. There was no significant trend in mortality rates in the 10 and 33 µg/kg/day dose fentanyl treated males (Groups 3 and 4) compared to either control group separately, or to the combined controls. There was a significant increase ($p < 0.05$) in mortality in the 10 µg/kg/day group versus control group 2 or combined controls by both Cox-Tarone and Gehan-Breslow tests.

The Sponsor suggests that this increased mortality may not be treatment related because of the lack of any dose response or effect at the 33 µg/kg/day level, thus they considered the data to indicate there was no effect of fentanyl on male survival.

Reviewer Comment: The reviewer disagrees with this conclusion. While it is true that for these two fentanyl doses, there is no statistical increase in mortality, when one also considers the 100 µg/kg/day which exhibited increased mortality early in the study before the entire group was terminated, there is a definite dose effect of fentanyl on survival.

Females: Due to decreased survival (36% survival; n=20) in one of the females control groups (Group 1), this group was terminated on day 688 (week 99), and terminal sacrifice for all female groups was conducted during weeks 102/103.

Treatment with fentanyl HCl did not affect female survival. There was no difference in mortality of the two female control groups. There was a statistically significant positive trend in the mortality of the fentanyl treated groups (10, 33, and 100 µg/kg/day) compared to control female group 2 and a significant increase in mortality in the 100 µg/kg/day female group (based on the Gehan-Breslow method).

However, the Sponsor considered these effects to be not biologically meaningful because of the lack of dose response compared to the female control Group 1 or the combined control female groups.

Reviewer Comment: The reviewer disagrees with this conclusion as well for reasons presented above in the results for males.

The main cause of death from all groups was neoplasia, which included pituitary adenomas (males and females) and mammary gland fibroadenomas and carcinomas (females). These tumors were generally present with comparable incidence between the control and treated groups, with no evidence of increased neoplasia-related mortality associated with treatment. Tumor findings are discussed more thoroughly in the histopathology section. In many cases, no specific microscopic finding was associated with mortality, and the cause of death was undetermined. Nearly all other causes of death were related to miscellaneous neoplasms and inflammatory lesions, all of which occurred sporadically throughout the control and treated groups.

Reviewer Comment: As noted above, if the unintended mortalities (<week 36) in the 100 µg/kg/day male group are considered, there would be a dose response

relationship for increased mortality in the males. The 3-month dose-finding preliminary carcinogenicity study also had increased mortalities in the 100 and 200 µg/kg/day doses. Therefore in total, there would be a dose-response relationship for fentanyl-induced deaths for males and females. This is consistent with fentanyl's well characterized pharmacodynamic actions and well documented lethality in humans. In rats, there appears to be sex-related difference in susceptibility to the lethal effects of fentanyl, evident at some point between the doses of 33 and 100 µg/kg/day. A more significant point is whether there is a human correlate to this susceptibility. Current studies and literature do not provide an answer due to the lack of sufficient data or analysis to address the issue. Of particular concern for this study is whether the cause of death was due to tumors. For this, the data are limited to females, since most high dose males were sacrificed early and with only histopathological analysis of gross lesions. However, considering the pharmacodynamics of fentanyl, the time for typical drug-induced tumor to develop, and lack of fentanyl-related tumors as a cause of mortality in females, it is unlikely fentanyl-related tumor were developing at the time of sacrifice in the high-dose male group.

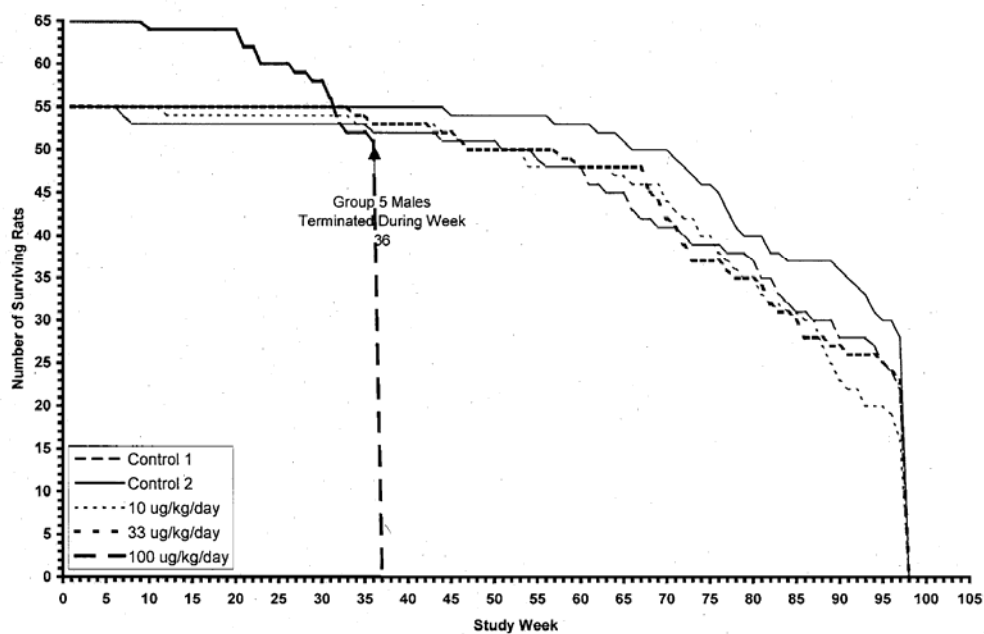
Table of Mortalities and Survivors

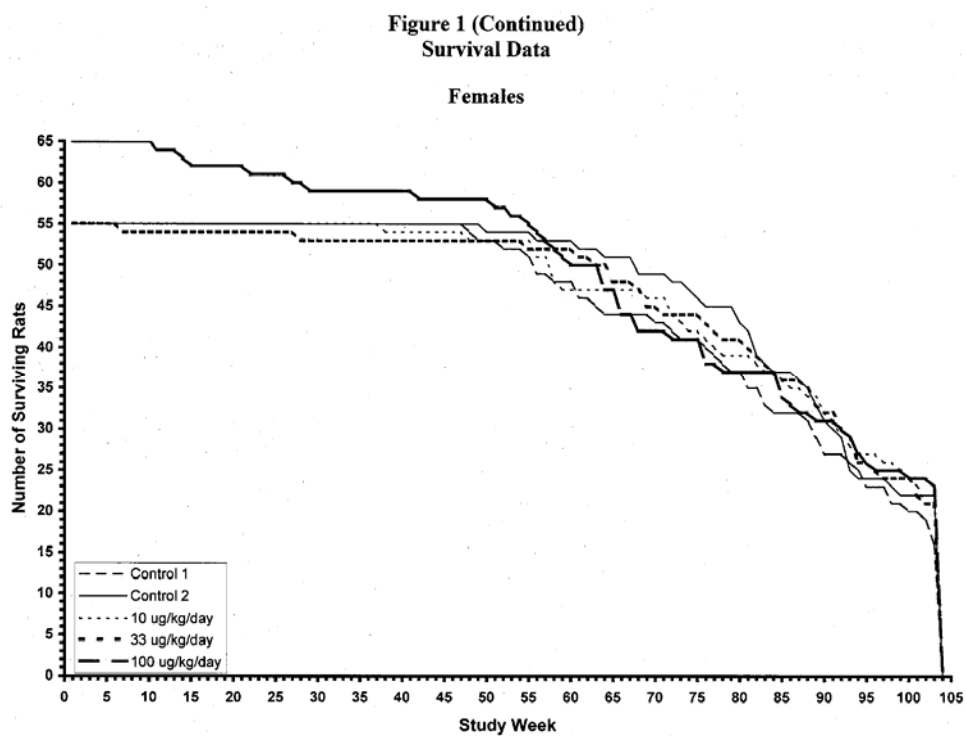
Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N =	55	55	55	55	65	55	55	55	55	65
Mortalities										
during year 1	4	1	5	5	All*	2	1	2	1	8
during year 2	29	26	34	27		37	32	32	33	34
Total mortalities (rounded values)	33	27	39	32	65*	39	33	34	34	42
	60%	49%	71%	58%	-	71%	60%	62%	62%	65%
Adjusted total mortalities; Kaplan-Meier estimates ± SE	60.0 ± 6.6	49.1 ± 6.7	70.9 ± 6.1	58.2 ± 6.7	-	70.9 ± 6.1	60.0 ± 6.6	61.8 ± 6.6	63.0 ± 6.6	64.6 ± 5.9
Survivors at termination (males: week 97; females: week 103)	Male study terminated at week 97					Females study terminated at week 102/103				
	22	28	16	23	-	16	22	21	21	23
	40%	51%	29%	42%	-	29%	40%	38%	39%	35%

* 14 animals dead by week 35 (21.5% mortality), sacrificed the 51 others during week 36

Figure 1
Survival Data

Males





Text Table 1
Results of Statistical Analyses of Survival Data for Male Rats

Group	1	2	3	4	5
Dose ($\mu\text{g/kg/day}$)	0	0	10	33	100
Unadjusted Mortality (Rate)	33/55 .600	27/55 .491	39/55 .709	32/55 .582	65/65 1
Adjusted Mortality:					
Kaplan-Meier Estimate (Final)	.600	.491	.709	.582	1
Standard Error	.066	.067	.061	.067	1

! All animals were dead/sacrificed by Week 36

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2 p (one-sided)	.1155 -	.0675 -
1 vs. 3-4 p (one-sided)	.3975 $\leq p \leq$.4155 -	.4398 $\leq p \leq$.4400 -
1 vs. 3 p (one-sided)	.2045 +	.2684 +
1 vs. 4 p (one-sided)	.4609 -	.4710 -
2 vs. 3-4 p (one-sided)	.1974 $\leq p \leq$.2110 +	.1125 +
2 vs. 3 p (one-sided)	.0117 + *	.0102 + *
2 vs. 4 p (one-sided)	.1245 +	.0612 +
1+2 vs. 3-4 p (one-sided)	.2597 $\leq p \leq$.2737 +	.1937 +
1+2 vs. 3 p (one-sided)	.0322 + *	.0423 + *
1+2 vs. 4 p (one-sided)	.2807 +	.1974 +
+ Effect in the increased direction		
- Effect in the decreased direction		
* Significant at 5.0% level		

Text Table 2
Results of Statistical Analyses of Survival Data for Females

Group	1	2	3	4	5
Dose ($\mu\text{g/kg/day}$)	0	0	10	33	100
Unadjusted Mortality (Rate)	39/55 .709	33/55 .600	34/55 .618	34/55 .618	42/65 .646
Adjusted Mortality:					
Kaplan-Meier Estimate (Final)	.709	.600	.618	.630	.646
Standard Error	.061	.066	.066	.066	.059

	Cox-Tarone Test	Gehan-Breslow Test
1 vs 2 p (one-sided)	.1478 -	.1130 -
1 vs. 3-5 p (one-sided)	.3131 $\leq p \leq$.3348 +	.1109 $\leq p \leq$.1110 +
1 vs. 3 p (one-sided)	.2120 -	.2068 -
1 vs. 4 p (one-sided)	.1928 -	.1379 -
1 vs. 5 p (one-sided)	.4966 -	.2666 +
2 vs. 3-5 p (one-sided)	.1039 $\leq p \leq$.1156 +	.0226 + *
2 vs. 3 p (one-sided)	.4624 +	.3761 +
2 vs. 4 p (one-sided)	.4936 +	.4808 +
2 vs. 5 p (one-sided)	.1485 +	.0377 + *
1+2 vs. 3-5 p (one-sided)	.2124 $\leq p \leq$.2292 +	.0570 +
1+2 vs. 3 p (one-sided)	.3821 -	.3850 -
1+2 vs. 4 p (one-sided)	.3530 -	.2746 -
1+2 vs. 5 p (one-sided)	.2791 +	.0749 +
+ Effect in the increased direction		
- Effect in the decreased direction		
* Significant at 5.0% level		
** Significant at 1.0% level		

Clinical signs: Animals were checked twice daily for mortality, abnormalities, and signs of pain and distress. Detailed observations were done once prior to initiation of treatment, weekly during the study, and on the day of scheduled sacrifice (Group 5 males and terminal-sacrificed females only). Weekly observations included mass palpation and mass data collection, including time of onset, location, progression, size, and appearance. Cageside observations were done approximately 1 and 4 hours postdose once at the end of the first week of study.

The 100 µg/kg/day male group (Group5) was terminated during week 36 due to behavioral changes characteristic of animals in distress (unthrifty appearance, markedly thinner than those of the other dose groups, inordinately sensitive to touch, and unusually aggressive). The incidences of malocclusions, thin appearance, aggressive behavior, hyperactivity, piloerection, and rough hair coat were all increased in the males of this group relative to the other dose groups. Also, the Group 5 rats appeared recumbent after each daily dose, and then were subsequently noted to be hyperactive prior to the next daily dose. During the first 6 months of the study, the clinical sign "hyperactivity" was noted in all fentanyl treatment groups, but with considerably higher incidence in the 33 and 100 µg/kg/day female groups. The incidence of malocclusions was higher in the 100 µg/kg/day female group.

Clinical Signs

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N =	55	55	55	55	65	55	55	55	55	65
Neurologic										
convulsions	2	2	1	1	0	1	1	4	2	2
tremors: head, limbs, or body	1	3	3	1	0	2	1	0	1	2
ataxic	5	6	8	8	0	20	18	13	12	5
circling	3	0	2	0	0	0	0	1	1	1
head tilt	4	0	3	3	0	8	9	7	7	2
hunched	6	7	14	10	2	11	18	8	10	9
hypoactive	13	17	16	13	2	29	21	14	12	3
hyperactivity	0	0	4	3	44	0	0	3	33	64
aggressive behavior	0	0	0	1	17	0	0	0	0	2
recumbent (lateral or sternal)	5	10	7	4	0	7	4	5	5	4
sensitive to touch	1	0	0	1	1	0	0	0	0	2
Eyes										
closed	1	0	0	1	0	0	0	0	0	0
discolored-reddish	1	0	0	0	0	0	1	0	0	0

opaque	1	1	1	0	0	1	3	1	1	15
pale	1	1	0	3	0	1	0	0	1	1
protruding	0	0	1	1	0	0	3	1	2	0
red discharge	13	15	14	10	19	37	30	25	22	40
squinted	7	7	12	6	1	13	12	9	6	7
swollen	1	3	0	0	0	0	3	0	2	0
Skin and Body Condition										
piloerection	0	0	0	1	13	0	0	0	0	0
rough hair coat	27	33	36	41	26	29	37	36	37	45
alopecia	2	5	6	9	2	2	8	13	12	16
thin appearance	13	13	17	15	6	22	21	17	20	22
malocclusions	9	10	12	15	34	8	6	12	10	45
mouth sore/scab	0	0	1	3	2	1	1	1	2	14
nasal discharge-red	17	19	19	11	6	16	18	12	11	12

Clinical Signs: Incidence of Observed Masses
(Reviewer created table from combined regions)

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N =	55	55	55	55	65	55	55	55	55	65
axillary region	1	0	1	0	0	12	13	26	23	13
head and cervical (dorsal and ventral)	0	1	3	4	0	5	3	8	3	2
inguinal	3	0	0	0	0	11	23	18	23	12
limbs and shoulder	0	1	1	0	0	1	2	2	1	0
tail	0	1	0	0	0	0	0	0	0	0
ventral abdominal	0	2	1	0	0	5	8	6	7	2
ventral thoracic	0	0	1	0	0	1	1	1	0	2
lateral (left and right)	0	1	0	2	0	0	2	2	1	0
wart-like lesion (all areas)	4	3	7	9	0	1	1	3	9	3

Body weights: Taken prior to initiation of treatment, once weekly during Weeks 1 through 14, and once every 4 weeks thereafter.

Males of the 100 µg/kg/day group had significantly ($p \leq 0.05$) reduced body weights (81%) compared to control males from throughout the study starting with

week 2. Males of the 33 µg/kg/day had significantly ($p \leq 0.05$) reduced body weight for weeks 9 and 10, then consistently from week 14 to the end of the study (once monthly measurements). Toward the end of the study there was increased variability in the data partly attributed to a reduction in animal numbers per group, which made statistically significant differences less likely. For females significantly reduced body weights occurred at week 18 for the 100 dose group, at week 30 for the 33 dose group, and sporadically after week 46 for the 10 dose group (again associated with increased variability in the data partly attributed to a reduction in animal numbers per group).

Consistent negative weight gain occurred in the control group and Group 4 at week 66, Group 2 at week 74, Group3 at week 78, and Group5 at week 82.

Body Weight and Body Weight Change at Selected Times (Reviewer Table, modified from Sponsor tables)

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
Starting N =	55	55	55	55	65	55	55	55	55	65
Body Weights at selected weeks g and (% of the average of the control groups)										
Week 1	253	253	255	254	253	175	173	175	174	173
2	305	305	303	302	295 (97%)	196	194	196	196	193
3	349	345	345	344	330	217	215	218	217	211
8	482	485	480	473	439	282	278	283	278	275
9	498	504	499	485	450	289	286	292	285	281
10	512	519	515	499	463	293	291	297	291	290
14	560	566	568	543 (96%)	490 (87%)	314	309	316	307	302
18						328	322	324	316	308 (95%)
26						347	340	346	332	324
30						355	350	349	336 (95%)	328 (93%)
34	665	688	674	629 (94%)	536 (80%)	366	362	354	345	333
42						391	383	376	356	341
46						400	392	380 (96%)	363	346
50	715	741	714	662		406	404	389 (96%)	372 (92%)	350 (86%)
94	713	722	710	654 (91%)		446	420	421	418	381 (88%)
102						426	400	399	401	377 (91%)

* Numbers is bold were significantly different from the combined control groups

Food consumption: Measurements were taken weekly during Weeks 1 through 13 and once every 4 weeks thereafter. The weight of food in the feeding bins at the beginning and end of each measurement week was used for calculating the food consumption of each animal, which was then averaged for the dose group for each measurement week.

The 100 µg/kg/day males (Group 5) had consistently lower food consumption values than the control groups for weeks 1 to 7 and weeks 12 to 33 (last week of data). The Sponsor indicated only that lower food consumption in the high dose males occurred beginning approximately at week 12. From week 29 to the study termination the 33 µg/kg/day males (Group 4) also had many incidences of reduced food consumption compared to the controls. The 100 µg/kg/day females (Group 5) also had times of reduced food consumption compared to controls, but these tended to be sporadic without consistent trends.

Reviewer Comment: Clarification of how food consumption was determined was provided the Sponsor on May 30, 2008. Due to weekly consumption and the offset of measurement weeks with body weight does not facilitate conclusions about the relationship between body weight changes and food consumption. In addition the wide variation in values probably reflects not only variation in food consumed, but also stereotypic behavior associated with fentanyl such as licking and gnawing, in which food is depleted from the food bin but is not ingested.

Food Consumption (g per week, and % of the average of the control groups;

Reviewer created table)

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
Starting N =	55	55	55	55	65	55	55	55	55	65
Week 1	218	217	213	213	204 (94%)	155	151	155	151	150
7	253	255	247	249	239					
10	243	243	244	244	239	183	176	181	179	186
12	243	246	246	250	224 (92%)					
33	255	238	241	231 (94%)	207 (84%)					
49	240	248	246	253		184	181	204	181	173
61						195	151 (77%) ^a	157 (80%) ^a	175	171
93	219	240	244	227		193	195	191	191	171 (88%)
101						180	173	186	175	172

* Numbers in bold were significantly different from the control groups

^a compared to Group 1

Hematology, Clinical Chemistry, and Urinalysis: Samples were obtained from 10 rats/sex/group at weeks 53, 97 (males only), and 103 (females only). In addition to the 10 rats/sex/group, blood was collected from all other surviving rats prior to scheduled sacrifice for select hematological tests. For the 100 µg/k/day Group 5 males terminated early, samples were collected from the first 15 males randomized for necropsy.

Reviewer comment: Values were obtained from about 20% of the animals at year 1 and about 30% of the animals at year 2. The basis for animals selection, if it was random or otherwise was not mentioned.

Based on week 36 samples in 100 µg/kg/day males (Group 5), there were no significant effects of fentanyl treatment on hematology, clinical chemistry or urinalysis findings. For the other treatment groups with samples collected at 1 year and 2 years of treatment, fentanyl did not cause any obvious or adverse effects on hematology, clinical chemistry or urinalysis at any dose level or interval. Although urine specific gravity values tended to be mildly lower and urine volume values tended to be mildly greater than those of control rats for 33 µg/kg/day male group during week 97 and 10 and 33 /kg/kg/day female groups during week 103, There was no clear dose-related pattern. The biological relevance of these differences from control is unclear.

Reviewer's comment: Summary mean values were not provided, for individual animals, there were few animals in which samples were collected for both year 1 and year 2, which would provide the most meaningful values for interpretation. For specific gravity, samples ranged from see table

Urinalysis										
Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N =	55	55	55	55	65	55	55	55	55	65
Specific gravity										
week 53	1.034-1.061	1.028-1.051	1.025-1.046	1.027-10.44	week 36 1.025-1.060	1.017-1.052	1.022-1.040	1.018-1.042	1.014-1.030	1.018-1.043
week 97	1.013-1.049	1.011-10.47	1.024-1.055	1.010-1.037		1.023-1.054	1.023-1.035	1.016-1.053	1.014-1.038	1.026-1.049

Gross pathology: A necropsy was done on each animal that died or was sacrificed at an unscheduled interval. Group 5 males were terminated early during week 36 (day 246 or 247). Terminal sacrifice for males was conducted during week 97 (days 674 and 675), and for females during week 102/103 (days 712, 717, and 718). Prior to scheduled

sacrifice, animals were fasted overnight, bled for clinical pathology, then anesthetized with sodium pentobarbital, exsanguinated, and necropsied. Bone marrow smears were made from the femur of all animals at the terminal schedule necropsies. At early termination for Group 5 males, bone marrow smears were made from the femur of the first 15 males randomized for necropsy.

Nearly all macroscopic findings noted at necropsy were generally considered nonspecific changes by the Sponsor and were typically seen in old rats and unrelated to fentanyl treatment. The only exceptions were the decrease in the occurrence of enlarged or mottled pituitary glands in the 100 µg/kg/day female group (which correlated with the decrease in pituitary neoplasia noted microscopically) and the higher incidence of external opaque eyes in the 100 µg/kg/day female group (which correlated with the corneal mineralization/epithelial degeneration noted microscopically).

Gross Pathology Findings

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N =	55	55	55	55	65	55	55	55	55	65
Eyes										
corneal mineralization					6					11
Brain										
mineralization					12			1		3
necrosis					12			1		4

Histopathology: Peer review: Yes, performed by another Covance pathologist. The methods indicated that tissues were processed from the first 15 males for early terminated Group 5 males and only lesions were processed from the remaining animals of this group. However the individual animal data tables indicate that all group 5 males were examined. The cause of death for all animals was documented by the anatomic pathologist in order to perform tumor analysis.

NON-NEOPLASTIC:

There was no microscopic evidence of changes specifically related to fentanyl HCl at the subcutaneous injection sites. Most of the microscopic findings were considered typical incidental and spontaneous changes commonly seen in aged rats and occurred unrelated to treatment with fentanyl HCl.

In the 100 µg/kg/day male group terminated early (week 36) the main histopathologic changes occurred in the lung, brain, and eye described below. These findings were likely related to the pharmacologic properties of fentanyl. Pathological changes of brain and eye were also observed in the 100 µg/kg/day female group terminated at week 102/103.

Lung: Giant cell pneumonia associated with foreign (plant, feed-like) material was a notable histopathologic change present with a very high incidence in the lungs. This change was graded slight to moderate and was morphologically characterized by the presence of feedlike plant material in alveolar spaces associated with an inflammatory response comprised of macrophages, multinucleated giant cells, and neutrophils. This finding is compatible with an aspiration of feed material.

Brain mineralization/necrosis occurred in 12 of the 100 µg/kg/day males that were sacrificed at week 36. This change was graded minimal to slight in most, moderate in two and moderately severe in one of the affected males. Mineralization/necrosis was most frequently present in the thalamic region of the brain (often bilateral) and, to a far less degree, the hippocampus. In Males B61220 and B61259, necrosis involving the cerebral cortex was a major component of brain necrosis. Although considered treatment-related, the Sponsor contends the role of fentanyl in the occurrence of these changes in the brain is unclear. Specifically, it is unclear as to whether this represents a primary effect of fentanyl or a secondary change possibly a response from hypoxia, since fentanyl is a respiratory depressant.

Necrosis was also present in the brain of three Group 2 control male rats necropsied at the 2-year termination of the study (B61047 in the cerebral cortex, B61056 in the thalamus and brain stem, and B61060 in the cerebellar cortex).

Mineralization/necrosis was also present in the brain of three 100 µg/kg/day females and one 10 µg/kg/day female sacrificed at the study termination. Necrosis was also present in the cerebral cortex of one 100 µg/kg/day female. As compared to the 100 µg/kg/day males (sacrificed at Week 36), the overall incidence of these brain findings in the Group 1-4 rats and Group 5 females was low. Additionally, several of these rats had concurrent lesions, including pituitary tumors, severe nephropathy, widespread organ necrosis, and polyarteritis. Therefore, the occurrence of brain lesions in the 10 and 100 µg/kg/day female groups, as well as the Group 2 male controls, may represent an incidental change unrelated to treatment with fentanyl, unlike the 100 µg/kg/day males where this finding appears more likely to be related fentanyl (cerebral hypoxia resulting from respiratory depression).

Eye: Corneal mineralization/epithelial degeneration occurred in the eyes. There was an increased incidence in males (6/65) and females (11/65) in the 100 µg/kg/day dose groups. These changes (graded as minimal to slight) occurred as a focal lesion in the center of the cornea and were characterized by mineralization of the subepithelial membrane associated with degeneration of the overlying corneal epithelium. The Sponsor suggests this finding may be related to dry eye.

Other Findings: A variety of other microscopic changes were present in rats from all groups that are considered typical incidental and spontaneous changes commonly seen in aged rats and unrelated to treatment with fentanyl.

Non-Neoplastic Lesion (from table)

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N	55	55	55	55	65	55	55	55	55	65
Eye										
corneal mineralization/ epithelial degeneration					6					11
Brain										
mineralization					12			1		3
necrosis		3			12			1		4

Reviewer's Comment: If the explanation of brain hypoxia/ischemia for the brain mineralization and necrosis findings as provided by the Sponsor is correct, it would be difficult to assess this in patients. It did require a substantial and prolonged dosing regimen to produce this effect. In patients, this would likely become evident through altered behavior and cognition. It would unlikely be recognized by the patient himself, and if pain is still present, it may not even be considered overdosing. A safety margin for the occurrence of brain mineralization/necrosis can be estimated based on previous toxicology studies containing toxicokinetic data assuming a linear dose-TK relationship. As indicated in the table below, for a patient dose of 1200 µg, a safety margin would not exist. (b) (4)

The noted AUC value for humans is for the highest dosing regimen that pharmacokinetics has been studied.

Safety margin for brain mineralization

Effect	NOAEL Dose	Rat AUC	Human
brain mineralization and necrosis	33 µg/kg/day	For 100 µg/kg/day: 30-50 ng-h/mL For 50 µg/kg/day: 19 ng-h/mL Therefore estimate for 33 µg/kg/day: 8-12 ng-h/mL (based on Alza study TR-01 5715-24)	Study C25608/1037 for a 1200 µg dose (2 x 600 µg), mean AUC _{0-∞} = 13.2 ng-h/mL

NEOPLASTIC:

The most frequent neoplasms noted microscopically included pituitary gland adenomas, adrenal medullary pheochromocytomas, thyroid C-cell adenomas and mammary gland fibroadenomas and carcinomas (females). These are commonly seen in Sprague Dawley rats, and there was no increased incidence associated with fentanyl treatment. However, statistical analysis of the incidence of neoplasms indicated several instances where statistically significant trend and group differences occurred.

Males: There was no fentanyl-related adverse carcinogenic response in the two male dose groups. Statistically significant effects and trends occurred for a reduction in occurrences for the following findings:

Epididymis/testis malignant mesothelioma (negative trend, $p=0.0163$ with the 10 $\mu\text{g/kg/day}$ at marginally reduced incidence compared to control Group 2, $p=0.0484$)

Thyroid follicular cell tumors, combined adenoma and carcinoma (negative trend versus control Group 2, with an associated decrease in the 33 $\mu\text{g/kg/day}$ group, $p=0.0252$).

Females: There were several cases of statistical significances noted.

Adrenal cortex adenoma: The 10 $\mu\text{g/kg/day}$ group had adrenal cortex adenoma increase over the combined control groups ($p=0.0209$). For the combined adenoma and carcinoma incidences in adrenal cortex, the 10 $\mu\text{g/kg/day}$ showed significant increase over the control group 1, 2 and the combined control ($p = 0.0292, 0.0229, 0.0031$, respectively).

Pituitary adenoma/carcinoma: There was a significant negative trend in the pituitary adenoma and the combined adenoma/carcinoma rate over control group 1 and 2 individually and the combined controls. All of the groups had significant decreases over control group 1 and the 100 $\mu\text{g/kg/day}$ group alone showed significant decrease over control group 2 and the combined controls. Also, control group 2 showed significant decrease ($p=0.0279$) over control group 1 for this case.

Mammary carcinoma: There was a statistically significant negative trend versus control groups 1 and 2 individually or combined ($p=0.0008, p=0.0173$, and $p=0.0095$, respectively), with a decrease in the 100 $\mu\text{g/kg/day}$ group compared to control group 1 or combined controls ($p=0.0020$ versus control group 1, $p=0.0147$ versus combined controls). The 10 $\mu\text{g/kg/day}$ and 33 $\mu\text{g/kg/day}$ groups showed marginal increases over control group 2 ($p=0.0411, p=0.0078$ respectively) and the 33 $\mu\text{g/kg/day}$ also showed significant increase over the combined controls ($p=0.0309$). When the carcinoma incidences were combined with the fibroadenoma incidences, the trends were still negative versus control group 2 ($p=0.0317$) and combined controls ($p=0.0382$), but becomes positive versus control group 1 ($p=0.0388$). All the significant group comparisons disappeared in the combination.

This strain of rats has high background incidences in the female mammary tumors. The rates in this study are well within the background (13.33%-62.31% for fibroadenoma and 8.57%-58.33% for carcinoma). Because of that and also because of the inconsistent trends and lack of significant increases over controls,

these spurious mammary findings are not deemed to be treatment related. *The reviewer concurs.*

Uterine endometrial stromal polyp: There was a significant positive trend over control group 2 (p=0.0380) or the combined controls (p=0.0297) for an increased incidence of uterine endometrial stromal polyps. The 10 µg/kg/day and 100 µg/kg/day groups had significantly more incidences of uterine endometrial stromal polyps than control group 2 or the combined controls (10 µg/kg/day: p=0.0428, or p=0.0452; 100 µg/kg/day: p=0.0200, or p=0.0137 vs control group 2 or combined controls, respectively).

This is also a common finding (with background rate of 0.91 %-11.67%) were not in a dose-related fashion and therefore, are considered to be background variations for this strain of rat. *The reviewer concurs.*

Neoplastic Lesion (Reviewer modified Sponsor Table 3)

Gender	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (µg/kg/day)	0	0	10	33	100	0	0	10	33	100
N	55	55	55	55	65	55	55	55	55	65
Adrenal Cortex										
adenoma						0	0	4	0	0
carcinoma						0	0	0	1	0
Adenoma+carcinoma						0	0	4	1	0
Adrenal Medulla										
Pheochromocytoma benign	3	6	6	4	0	5	1	3	2	3
Pheochromocytoma malignant	0	1	0	0	0					
Pheochromocytoma Benign+malignant	3	6	6	4	0					
Mammary										
fibroadenoma						13	23	20	15	19
carcinoma						14	7	16	19	3
fibroadenoma+carcinoma						24	28	30	28	21
Uterus										
endometrial stroma polyp						1	0	3	0	4
Pituitary										
adenoma	29	32	24	28	1	51	44	43	43	32
carcinoma						0	0	0	1	0
adenoma+carcinoma						51	44	43	44	32
Epididymis/Testis										
malignant mesothelioma	0	3	0	0	0					
Interstitial cell tumor	0	2	0	1	0					

Thyroid										
C-cell adenoma	3	4	5	7	0	3	4	7	4	4
C-cell carcinoma	2	2	0	2	0	0	0	0	0	1
C-cell adenoma+carinoma	5	6	5	9	0	3	4	7	4	5
follicular cell adenoma	0	2	2	0	0	0	0	1	0	1
follicular cell carcinoma	0	2	0	0	0	0	1	0	1	1
follicular cell adenoma+carcinoma	0	4	2	0	0	0	1	1	1	2

Kidney										
tubular cell adenoma	0	2	0	0	0					
Liver										
hepatocellular carcinoma	0	2	1	0	0					
Pancreas										
islet cell adenoma	3	1	2	4	0	1	0	0	2	0
islet cell carcinoma	1	0	0	1	0					
islet cell adenoma+carcinoma	4	1	2	4	0					
Hemato Neoplasia										
lymphoma	0	1	0	2	0	1	0	0	2	0
histiocytic sarcoma	2	0	2	2	0					

Toxicokinetics: No samples for toxicokinetic analysis were collected

Histopathology inventory

Study	TR-02-5715-021
Species	Rat
Adrenals	X
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X
Cecum	X
Cervix	
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	X
Heart	X
Ileum	X
Injection site	X
Jejunum	X
Kidneys	X
Lachrymal gland	
Larynx	
Liver	X
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	X
Ovaries	X
Pancreas	X
Parathyroid	X
Peripheral nerve	X
Pharynx	
Pituitary	X
Prostate	X
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X

Spinal cord	X
Spleen	X
Sternum	X
Stomach	X
Testes	X
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X
Zymbal gland	X

X, histopathology performed

*, organ weight obtained

Summary Carcinogenicity Study Results:

A two year carcinogenicity study in rats was conducted in rats. Subcutaneous administration of fentanyl HCl at daily single doses of 10, 33 or 100 µg/kg/day in females and at dose levels of 10 and 33 µg/kg/day in males did not result in an increased incidence of neoplastic lesions. Males in the 100 µg/kg/day dose group were sacrificed at week 36 due to a higher than expected incidence of mortality and also aggressiveness and were not included in the final carcinogenicity analysis, although they also had no increased incidence of tumors at the time of sacrifice.

Notable other findings included brain mineralization/necrosis that occurred in 12 of 65 males in the 100 µg/kg/day dose group. This change was graded minimal to slight in most, moderate in two and moderately severe in one of the affected males. Mineralization/necrosis was also present in the brain of three 100 µg/kg/day females and one 10 µg/kg/day female sacrificed at the study termination. Necrosis was also present in the cerebral cortex of one 100 µg/kg/day female. It is unclear as to whether this represents a primary effect of fentanyl or a secondary change possibly a response from hypoxia, since fentanyl is a respiratory depressant.

Corneal mineralization/epithelial degeneration occurred in the eyes with an increased incidence in males (6/65) and females (11/65) in the 100 µg/kg/day dose groups. These changes (graded as minimal to slight) occurred as a focal lesion in the center of the cornea and were characterized by mineralization of the subepithelial membrane associated with degeneration of the overlying corneal epithelium. This may be associated with persistent dry eye.

Giant cell pneumonia associated with foreign (plant, feed-like) material was a notable histopathologic change present with a very high incidence in the lungs. The finding was compatible with an aspiration of feed material, evident in alveoli histopathology.

Carcinogenicity Recommendation: The Sponsor may add this information to their label. Since toxicokinetics was not available in this study, there may be other studies conducted with similar doses that would provide a reasonable estimate of exposure for calculating exposure margins between this study and clinical exposure levels.

APPENDIX 2: RESIDUAL MONOMER TOXICITY SUMMARY

^{(b) (4)}: Toxicity Assessment

1. Toxicity evaluation of residual monomers from the literature

- a. ^{(b) (4)}
- b. ^{(b) (4)}
^{(b) (4)}

2. Discussion and Conclusion

3. References

1. Toxicity evaluation of residual monomers from the literature

a

(b) (4)

(b) (4)

Human adverse reaction findings

There are several case reports of the dermal and the ocular irritation in human at (b) (4) ppm (b) (4) from the occupational exposure to (b) (4) a few cases of sensitization associated with blister formation were also reported in human.

Nonclinical toxicity findings

ADME: (b) (4) was found to be readily absorbed and widely distributed in the body when administered orally and via inhalation. No ADME studies with dermal route of administration could be located. (b) (4) irrespective of its the route of administration is thought to be hydrolyzed by esterases to an unstable metabolite called (b) (4)

Genotoxicity: Negative in Ames test, positive in chromosomal aberration in human lymphocytes, and in vivo micronucleus assay (b) (4)

Carcinogenicity: In the rat 104-week carcinogenicity bioassay via inhalation showed squamous cell carcinoma, and nasal tumors at high dose. A LOAEL of (b) (4) was established from this study (b) (4)

Reproductive and developmental toxicity studies (b) (4) after oral route of administration resulted in a decrease F₁ pup size and growth retardation (b) (4). A LOAEL of (b) (4) was established based on this study.

Neurological toxicity associated with hunched posture, ruffled fur, and head tilting was noted after the exposure of (b) (4) by inhalation. A LOAEL of (b) (4) in rat and mice were established from this study (b) (4) Chronic toxicity and

carcinogenicity study with (b) (4) in drinking water was also conducted in rat. No carcinogenicity was observed up to 250 mg/kg.

Immunological toxicity assessed by decrease in weight of thymus and spleen was observed after inhalation as well as oral exposure of (b) (4) in mice and rat. A LOAEL of (b) (4) was established (b) (4)

(b) (4) applied to the skin of rabbit resulted in erythema, edema, and necrosis of skin; however, the dose/concentration applied was not mentioned (b) (4)

In mice and rat, airway irritation was the major toxicity observed after exposure to (b) (4) via inhalation, based on this finding a NOAEL of (b) (4) was established in mice. A minimal risk level (MRL) of (b) (4) is calculated in human based on the air way irritation finding in the nonclinical studies (b) (4)

Reviewer's comments: The toxicity information on (b) (4) was extracted from the publicly available database. The reviewer noted that nasal irritation was the only toxicity observed at low dose (NOAEL (b) (4) ppm) based on which EPA has established the minimal risk level from inhalation. At higher dosages and mainly with the inhalation route of administration (b) (4) was observed to induce squamous cell carcinoma in rats; no such findings have yet been identified in human. Followings are the toxicity summary tables compiled from the ATSDR review on (b) (4)

TABLE 2-5. Genotoxicity of (b) (4) In Vitro

Species (test system)	End point	Results		References
		With activation	Without activation	
Prokaryotic organisms:				
<u>Salmonella typhimurium</u> TA98, TA100, TA1530	Gene mutation	-	-	Bartsch et al. 1976, 1980
<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537, TA 1538	Gene mutation	-	-	Florin et al. 1980; Lijinsky and Andrews 1980; McCann et al. 1975
<u>S. typhimurium</u> TA1530, TA100	Gene mutation	-	-	Bartsch et al. 1979
<u>S. typhimurium</u> TA100	Gene mutation	-	-	Barbin et al. 1978
Mammalian cells:				
Cultured human lymphocytes	Micronuclei	No data	+	Maki-Paakkanen and Norppa 1987; Norppa et al. 1988
Cultured human lymphocytes	Chromosomal aberrations	No data	+	Jantunen et al. 1986; Norppa et al. 1985;
Cultured human lymphocytes	Sister chromatid exchange	No data	+	He and Lambert 1985; Norppa et al. 1985
Cultured human lymphocytes	DNA cross-links	No data	+	Lambert et al. 1985
Cultured hamster fetal cells	Adenovirus transformation	No data	+	Casto 1980, 1981
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Norppa et al. 1985

DNA = deoxyribonucleic acid; - = negative result; + = positive result

TABLE 2-6. Genotoxicity of (b) (4) In Vivo

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse spermatogonial cells	Meiotic micronucleus assay	-	Lahdetie 1988
Rat hepatic cells	DNA-adducts	-	Simon et al. 1985b
Mouse bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	+	Maki-Paakkanen and Norppa 1987; Norppa et al. 1988; Hazleton 1979d
		-	Hazleton 1979b, 1980b
Rat bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	-	Hazleton 1979c, 1979d, 1980c
Mouse bone marrow	Sister chromatid exchange	+	Takeshita et al. 1986

DNA = deoxyribonucleic acid; - = negative; + = positive

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Inhalation Toxicity Studies

TABLE 2-1 (Continued)

Key to figure*	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
27	Rat	104 wk 5d/wk 6hr/d	Resp	50	200	(increased relative lung weight; olfactory atrophy)	Hazleton 1988b
			Gastro	600			
			Cardio	600			
			Hemato	600			
			Hepatic	600			
			Renal	600			
			Other		600	(decreased body weight gain)	
28	Mouse	104 wk 5d/wk 6hr/d	Resp	50	200	(airway irritation, hyperplasia, nasal and tracheal lesions)	Hazleton 1988b
						600 (increased lung weight; exfoliation of bronchial epithelium; fibro-epithelial tags; histiocyte accumulation)	
			Gastro	600			
			Cardio	600			
			Hemato	600			
			Hepatic	600			
			Renal	600			
			Other		600	(decreased body weight gain)	
Immunological							
29	Rat	104 wk 5 d/wk 6 hr/d			50M	(decreased relative spleen weight)	Hazleton 1988b
Neurological							
30	Rat	104 wk 5 d/wk 6 hr/d			50	(hunched posture; ruffled fur; head tilt)	Hazleton 1988b
31	Mouse	104 wk 5 d/wk 6 hr/d			50	(hunched posture; ruffled fur; head tilt)	Hazleton 1988b

TABLE 2-1 (Continued)

Key to figure*	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
Cancer							
32	Rat	104 wk 5d/wk 6hr/d				600 (nasal cavity tumors)	Hazleton 1988b

Oral Toxicity Studies:

Key to figure ^a	Species	Route	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological								
19	Rat	(W)	104 wk 7d/wk		235			Hazleton 1988a
Developmental								
20	Rat	(W)	2 generations		117	431 (decreased F1 pup weight gain)		Hazleton 1987
Reproductive								
21	Rat	(W)	2 generations		431			Hazleton 1987

^aThe number corresponds to entries in Figure 2-2.

Dermal Toxicity Studies:

TABLE 2-3. Levels of Significant Exposure to (b) (4)

~~Dermal~~

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference
				Less serious	Serious	
ACUTE EXPOSURE						
Death						
Rabbit	1 d 24hr			8.0 mL/kg	(LD50)	Weil and Carpenter 1969
Rabbit	1 d 24hr			2.5 mL/kg	(LD50)	Smyth and Carpenter 1948
Systemic						
Human	1 d 48-72 hr	Derm/oc	2X			Tanaka and Lucas 1984
Rabbit	4-72 hr	Derm/oc	0.5 mL	(slight edema)		Industrial Bio-Test Laboratories 1972
Rabbit	1 d 24hr	Derm/oc	8.0 mL/kg	(erythema, edema, necrosis)		Weil and Carpenter 1969
Rabbit	1 d 1x/d	Derm/oc	0.5 mL	(minor corneal injury)		Weil and Carpenter 1969
INTERMEDIATE EXPOSURE						
Systemic						
Rat	15 d 6hr/d	Derm/oc	(b) (4) ppm ppm	(eye irritation)		Gage 1970

d = day; Derm/oc = dermal/ocular; hr = hour; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; NOAEL = no-observed-adverse-effect level; 1x = one time

b

(b) (4)

(b) (4)

Human adverse reaction findings

There were seven confirmed cases of allergic contact dermatitis due to the use of (b) (4) in the adhesive tapes. A few cases on contact urticaria due to the use of (b) (4) in Europe were also reported at an exposure level of (b) (4) ppm. No other reports of adverse findings in human with (b) (4) are available (b) (4)

Non clinical toxicity findings

ADME: (b) (4) absorbed systemically when administered via inhalation, oral, and intraperitoneal route (no data for dermal administration is available). It has been shown to be metabolized into (b) (4)

(b) (4) It also reacts with (b) (4) such as (b) (4) causing depletion of (b) (4) groups and formation of (b) (4) which is eliminated via urine. Higher than 90% excretion was observed at 72 hrs.

Genetic toxicity: (b) (4) was observed to be negative in Ames test and *in vitro* chromosomal aberration assays, positive sister chromatid exchange assay (b) (4)

Carcinogenicity: Three toxicity studies using (b) (4) have been identified which demonstrated carcinogenicity findings in mice. In one of those studies, solutions of 2.5, 21, and 86.5% (b) (4) in acetone were topically applied to a group of 80 male mice 3 x/week throughout their life time. No neoplasms were observed at 2.5% group (approximately 666.6 µg/day). With 21 and 86.5% (b) (4) severe skin irritation was associated with benign and malignant skin tumors, hyperkeratosis, scabs, thickened subcutaneous tissue, papillomas, cornified squamous cell carcinomas, malignant melanomas, fibrosarcomas, and dermal hyperplasia. All these findings suggest that the carcinogenicity findings might be secondary to irritation and not due to the direct effect of (b) (4). In another carcinogenicity study with (b) (4) (75%) in acetone when applied topically in male mice for 6-months, 2/40 treated animals developed squamous cell carcinomas and 4/40 treated animals showed squamous cell papillomas. In an additional study, 86.5% (b) (4) solution in acetone when topically applied in mice (male, 40/group), 2/40 developed malignant skin carcinoma; 1/40 from the vehicle control group had similar findings. All these

carcinogenicity findings identify (b) (4) as a hazardous material at high dose

Reproductive and developmental effects: (b) (4) a metabolite of (b) (4) is known to cause developmental defect like thalidomide in rats at 800 mg/kg. (b) (4) administered to rat during gestation caused a decrease in maternal body weight but no teratogenicity was observed (b) (4)

Dermal contact hypersensitivity was noted in guinea-pigs w/0.17 M challenge dose administration (Danish EPA, 2005).

Dermal irritation was noted in mice (NMRI) treated with 86.5% (b) (4) treated dermally for longer than 2 weeks. Dermal inflammation was noted in rabbits exposed to 1 mL of (b) (4), necrosis and ulceration was observed after 12 days of chronic exposure.

Systemic toxicity finding include chronic nephritis (68% increase compare to control) findings in C3HJ mice treated dermally with (b) (4) (20 mg, 75% v/v) for more than 6 month. 3-month inhalation toxicity study in the Wistar rat showed reduced body weight gain, lethargy, irritation, and degeneration of olfactory cells in the nasal mucosa.

Reviewer's comments: Based on the above mentioned findings, a NOAEL of (b) (4) was established by EPA. A minimal risk level (MRL) of (b) (4) ppm is calculated in human based on the nasal irritation findings in the non clinical studies by EPA. The reviewer agrees on the minimal risk findings from EPA. Note that no adequate reproductive toxicity studies were conducted.

c

(b) (4)

(b) (4)

Human adverse reaction findings

There are several case reports of skin sensitization resulting from occupational exposure to (b) (4). Some of these studies indicate that (b) (4) is a (b) (4) and may interact with other acrylates in some exposed individual.

Non clinical toxicity findings

ADME: The metabolism and excretion of (b) (4) has been examined in Fisher rats using oral, intraperitoneal, dermal, and inhalation exposure. Irrespective of route of administration, (b) (4) has been observed to be (b) (4).

Genetic toxicity: Genotoxicity studies with (b) (4) revealed that it is not mutagenic without metabolic activation in the AMES test. (b) (4) however, was observed to be positive (b) (4) fold increase in revertants as compared to controls) at 1.25 mg/plate and above in *E. coli* strain WP2/pKM101 and at 2.5 mg/plate and above in strain WP2 uvrA/pKM101 (b) (4) in the presence of metabolic activation in the AMES test. (b) (4) also reported a dose related increase (0, 15, 18, and 20 µg/mL concentrations tested) in chromosomal aberrations and micronuclei in L5178Y mouse lymphoma cells treated with (b) (4) in the absence of (b) (4).

Carcinogenicity: An inhalation carcinogenicity study in rat produced a NOAEL of (b) (4) ppm (OECD, SIDS, 2005).

Reproductive and developmental toxicity: There are no reports of reproductive and developmental toxicity studies in the publicly available database. The histopathology findings of the reproductive organs from the long-term toxicity studies in rat and dog did not show any test article related adverse effects (OECD, SIDS, 2005).

General toxicity: Sub acute toxicity studies w/ (b) (4) established an oral LD₅₀ of 540 mg/kg in rat. Clinical signs following the administration of 10% aqueous solution included hypo activity, rough fur, labored breathing, muscle weakness and GI tract hemorrhage. Repeated exposure to vapor of (b) (4) to rats via inhalation (7 hr/days, 5 days/weeks for 4-weeks) caused severe nasal irritation, resulting in death due to

respiratory failures; focal rhinitis was observed in sub lethal dose. Based on these findings a LOAEL of (b) (4) ppm was established. A chronic toxicity study in rat conducted for 18-months with (b) (4) ppm dosages of (b) (4) /day resulted on irritation of nasal cavity, no other systemic toxicity was observed (b) (4)

Dermal toxicity study showed that (b) (4) is severely irritating to skin at dosages (b) (4) ppm. It caused irreversible corneal injury. Skin sensitization was also noted in animals. Following is summary table of sensitization test which is reproduced from (b) (4)

Table 8 Sensitization Tests in Laboratory Animals

Species	Test method	Result	Reference
Mouse	Local Lymph Node Assay	Sensitization	Ashby et al., 1995 (Key Study)
Mouse	Local Lymph Node Assay	Sensitization	Scholes, 1992
Guinea pig	Maximization test 0.5% solution of HEA in a 9:1 mixture of Dowanol DPM:Tween 80.	Sensitization (10 of 10 animals)	Norris, 1970
Guinea pig	Buehler test Day 1, 3, 8, 10, 14 and 16: 50% HEA in 60 % acetone (0.5 ml) by dermal route Day 42: 50% HEA in 60% acetone (0.5 ml) by dermal route	Sensitization (10 of 10 animals)	Kapp, 1977
Guinea pig	Maximization test. Induction 10% solution of HEA in 97% ethanol. Challenge, 5% solution of HEA in 97% ethanol	Sensitization (10 of 10 animals)	Auletta et al, 1982 Report from Bio/dynamics Inc.
Guinea pig	Maximization test Day 0: in presence of Freund's Complete adjuvant (FCA), 0.5% HEA (50 µl) in sterile water i.p. Day 7, 8: HEA, 25%, (400 µl) by cutaneous route, Day 21: 0.3% (25 µl) in petrolatum on the flank, occlusive patch for 24 hours Evaluation: 48 and 72 hours after patch removing.	Sensitization (12 of 12 animals)	Clemmensen, 1984
Mouse	Local lymph node assay	Positive local lymph node response	Basketter and Scholes, 1992

Reviewer's comment: Based on the nonclinical toxicity evaluation mentioned above, the major toxicity findings associated with (b) (4) is skin irritation, nasal mucosal irritation, ocular injury (if contacted directly), and sensitization. Because there are similar finding in human, the nonclinical skin irritation, ocular irritation, and sensitization findings are believed to be biological relevant. A NOAEL of (b) (4) ppm is determined for carcinogenicity findings in rat. (b) (4) has found to be positive in AMES test in two strain of *E.coli*, indicating that it might be genotoxic. As this is a

genotoxic compound, exposure to (b) (4) via products containing (b) (4) should be limited to NMT 1.5 mcg/day.

Discussion and conclusion

(b) (4) is a random (b) (4) (b) (4)
It is considered as a new excipient because it would be used in a FDA approved drug product for the first time. Therefore, the reviewer believes that the specifications must be set for the residual monomers, degradation product/s, and residual solvents from (b) (4)

The reviewer believes that specification for the residual monomers would be established by the user of the final drug product. The specifications of the residual monomers must be based on the data derived from the extractable/leachable studies.

The toxicity assessment from the publicly available literatures showed that all of the components of (b) (4) are potentially irritating (mild-severe) in rat, rabbit, and human. (b) (4) are observed to be sensitizers in animals; this finding is considered biologically relevant because similar findings were noted in human. No NOAEL for sensitization could be established. No adequate reproductive and developmental toxicity studies are available with (b) (4). (b) (4) is carcinogenic in rodent in inhalation studies at (b) (4) ppm (caused nasal cell carcinoma), (b) (4) is carcinogenic in mice (68% in acetone) in mice dermal carcinogenicity study (caused neoplastic lesion in skin), and (b) (4) did not cause neoplasm in an inhalation carcinogenicity study in rat (18 month). The metabolisms of (b) (4) are rapid, no bioaccumulation noted, however, clinical reports indicate that both (b) (4) may cross react with other acrylates exposed to same individuals. All these findings need to be considered for risk assessment when the exposures of these monomers are anticipated from the same product.

This (b) (4) of the (b) (4) reaction (b) (4) as previously been used for different FDA approved products that contain (b) (4) adhesives. (b) (4) is used as (b) (4) for components of paper and paperboard in contact with food (b) (4) and for cross-linking (b) (4) intended for repeated use in contact with food, provided the (b) (4) content does not exceed (b) (4) weight percent (b) (4) ppm) of the finished resin (b) (4). Following is the structure of (b) (4) molecular weight (b) (4) CAS registry # (b) (4)

(b) (4)

Health Council of Netherlands evaluated toxicity of AIBN. Following paragraph is quoted from their findings:

(b) (4)

For example, the half-life time of (b) (4) is (b) (4) min. (ca. 70 days) at ca. 30°C, Whereas at 105°C, the melting point of (b) (4), the half-life time is only 4 min. In industrial processes (b) (4) is used at temperatures ranging between 100°C and 150°C. This shows that at a relatively mild temperature of 30°C only small amounts of the decomposition (b) (4) product are formed. In contrast, upon heating (b) (4) may be formed in larger quantities.

(b) (4)

(b) (4) Following is the structure of (b) (4) molecular weight (b) (4)

(b) (4)

The DMF-holder was requested to provide batch analyses data to estimate the range of (b) (4) present in (b) (4) in a teleconference dated May 15, 2009. DMF-holder, (b) (4) previously known as (b) (4), sent the table (dated May 20, 2009) reproduced as follows indicating that the range of the (b) (4) in different batches of the liquid raw material, (b) (4) varies between (b) (4) ppm.

Date of manufacture	Lot number	(b) (4) (ppm)
11/11/01	LLY407	Not measured
21/04/03	DCY153	(b) (4)
25/11/03	LCY428	
27/12/03	MCY469	
15/07/04	GDY268	
14/09/04	JDY356	
11/02/05	BEY055	
14/04/05	DEY150	
09/06/05	FEY221	
20/08/05	HEY353	
02/01/06	AFY006	
12/01/06	AFY023	
28/05/06	EFY254	
07/11/06	LFY536	
05/03/07	CGY111	
14/07/07	GGY353	
12/09/07	JGY459	
29/02/08	BHY109	
25/05/08	EHY257	
07/10/08	KHY527	
12/10/08	KHY538	
09/01/09	AJY014	
17/02/09	BJY066	
18/03/09	CJY104	
20/03/09	CJY114	
22/03/09	CJY115	

The DMF-holder also provided an assessment of the nonclinical toxicity studies with (b) (4) dated May 20, 2009. The toxicity assessment provided by the DMF holder include evaluation of the genotoxicity, carcinogenicity, sensitization, and reproductive toxicity. The toxicity assessment of these so called 'low dose' effect showed that (b) (4) is not genotoxic, no carcinogenicity studies were conducted with (b) (4), no sensitization study was conducted with (b) (4), and there is no NOAEL for (b) (4) between (b) (4) mg/k/day with intraperitoneal administration in hamster in the teratology study.

The QSAR analysis requested by the reviewer and conducted by the Computational toxicity group within FDA observed that (b) (4) was present in the training data sets for *Salmonella* mutagenicity and scored as inactive. (b) (4) was run against the remaining battery of genetic toxicity models using both the (b) (4) computational toxicology software programs. (b) (4) predicted the test compound to be negative at the following endpoints: *E. coli* mutagenicity, hgp_{prt}, and micronucleus *in vivo*. (b) (4) gave negative predictions for (b) (4) for all genetic toxicity endpoints

evaluated: fungal mutagenicity, rodent mutation *in vivo*, hprt-chromosome aberrations *in vivo*, micronucleus *in vivo*, and UDS. Based on this findings (b) (4) might be predicted to have minimal health hazard based on genotoxicity and carcinogenicity.

No sensitization study was conducted with (b) (4); however, (b) (4) containing product might be present in food and transdermal patches available in market.

Limited data exists for the reproductive toxicity assessment of (b) (4).

The nature of the fetal toxicity was not discussed in detail, only a reduction in the group-length was mentioned, but no NOAEL was established. (b) (4) is not classified as a developmental toxicant in EU (European Union) hazardous substance data base.

The repeat dose toxicity study with (b) (4) identified kidney toxicity in male rat (probably due to sex specific accumulation of α -macroglobulin) and liver toxicity in rat and dog. The NOAEL for kidney toxicity was established to be (b) (4) mg/kg/day and the NOAEL for the liver toxicity was established to be (b) (4) mg/kg/day.

All cases showed about the same symptoms. After inhalation exposed individuals became unconscious and had convulsions. Further investigations on workers employed at the same factory displayed that some symptoms were prominent in the group: frequent headaches, excessive salivation, and sense of taste, nausea, and vomiting.

Some information of biotransformation was reported after intraperitoneal, intravenous, and intratracheal injection of (b) (4) in rats. Free hydrogen cyanide (HCN) was found in the blood, the liver, the brain, and the lungs and was regarded as the basic cause of toxicity.

In metabolic studies in rats, (b) (4) was shown to give rise to little or no blood HCN levels or blood and urine isothiocyanate concentrations, indicating that (b) (4) is probably metabolized in the rat by a pathway that does not involve inorganic cyanide (b) (4). (b) (4) reported that uptake of (b) (4) occurs after inhalation and through the skin, but no quantitative data are available. There is no specific information on the metabolism and excretion of this compound. Since (b) (4) belongs to the group of organic compounds that contain a cyano group as the characteristic functional group, it can be surmised that the compound will undergo biotransformation to cyanide, which is further metabolized to thiocyanate.

An occupational exposure limit of (b) (4) mg/m³ (b) (4)-hours daily exposure) was established or recommended in the Netherlands, Germany, UK, and by the USA for (b) (4). A skin notation for (b) (4) had been added. Recently, the committee on Updating of Occupational Exposure Limits of the Health Council of the Netherlands has

recommended a HBR-OEL (Health Based Recommended Occupational Exposure Limit) for (b) (4) of (b) (4) mg/m³ (8-hour daily exposure). In its documentation, ACGIH stated that (b) (4) is a potent convulsant. A TLV-TWA (threshold limit value-time weighted average) of (b) (4) mg/m³ was proposed, in order to minimize the potential for systemic toxicity manifested in workers as headache, nausea, and convulsions. A skin notation was considered appropriate, because structurally related dinitriles were reported to cause mortality in dermally treated animals (ACGIH, 2001). (b) (4) was noted to be absorbed by the skin in rabbit (EPA, 1981).

Because of its high volatility (b) (4) is expected to (b) (4) during the (b) (4) however, the level of (b) (4) in the (b) (4) adhesive (b) (4) will depend on conditions used such as (b) (4) temperature, coating thickness etc. The supplier of (b) (4) developed a validated method for identifying the residual (b) (4). The levels of (b) (4) in different finished drug products would vary depending on the drying process of the differen (b) (4)

In conclusion, the raw material (b) (4) is recognized to contain (b) (4) and the impurities associated with potential (b) (4) of all of the above. Therefore, drug product containing (b) (4) should have specifications for the residual monomers and byproducts which are known to have toxic effect in non clinical studies and in human.

References

American Conference of Governmental Industrial Hygienists (ACGIH), 2000, TLVs® and BEIs®. Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati OH, USA; ACGIH, 43.

American Conference of Governmental Industrial Hygienists (ACGIH), 2001, TLV® and BEIs®. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 56.

(b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

IARC (International Agency for Research on Cancer)., 1995, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans . Dry Cleaning, Some Chlorinated Solvents and other Industrial Chemicals 63.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

APPEARS THIS WAY ON ORIGINAL

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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

/s/

MAMATA DE
07/29/2009

RICHARD D MELLON
07/29/2009

The reader is referred to the secondary review for further information regarding PMRs and PMCs.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 19-813/SCF-044	Submission Date(s): 01/30/2009
Brand Name	Duragesic™
Generic Name	Fentanyl Transdermal System
Clinical Pharmacology Reviewer	Rajanikanth Madabushi, Ph.D.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Division of Anesthesia, Analgesia and Rheumatology Products
Sponsor	Ortho-McNeil-Janssen Pharmaceuticals Inc.,
Submission Type; Code	NDA 505(b)(1); Priority (CMC Supplement)
Formulation; Strength(s)	Transdermal Matrix Patch
Proposed Indication	Management of persistent moderate to severe pain

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted in support of NDA 19-813/SCF-044 for D-TRANS matrix formulation for transdermal administration of fentanyl and found it acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Ortho-McNeil-Janssen Pharmaceuticals, Inc. (OMJPI) on behalf of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) is seeking approval of a revised formulation for transdermal delivery of fentanyl in the current supplemental New Drug Application (sNDA). DURAGESIC, a transdermal fentanyl reservoir system, is currently approved (in 1990) and marketed in the United States for the management of persistent, moderate to severe chronic pain.

ALZA Corporation has developed a transdermal fentanyl matrix system (D-TRANS matrix system), a drug in pressure-sensitive adhesive system, intended to overcome some of the inelegant and potentially unsafe characteristics of the reservoir system. This design eliminates the need for a rate controlling membrane and the controlled release of fentanyl is achieved by the stratum corneum of the skin. In the current submission the sponsor is seeking for the approval of D-TRANS matrix system (12.5, 25, 50, 75 and 100 µg/h) that is intended to replace DURAGESIC if approved.

The clinical pharmacology and biopharmaceutics program performed to support the D-TRANS matrix formulation included the following studies that were reviewed by this reviewer:

- A pivotal bioequivalence study, conducted to evaluate the pharmacokinetics of the D-TRANS fentanyl matrix system with the approved US DURAGESIC fentanyl reservoir system at the highest marketed dose strength of 100 µg/h.
- A pharmacokinetic study to evaluate the pharmacokinetics of fentanyl following single and repeated application.
- A dose proportionality study over the range of 25 µg/h - 100 µg/h.
- Studies to characterize the effect of age, skin types, site of application and application of external heat on fentanyl pharmacokinetics.

Additionally 3 more studies were conducted by the sponsor providing supporting BE information. The reference product in these studies was the EU approved DUROGESIC reservoir product. The EU DUROGESIC reservoir system, is reported to be compositional different compared to DURAGESIC. Since the composition of DUROGESIC is unknown, these additional studies were not reviewed.

The key clinical pharmacology and biopharmaceutics findings are:

- The 100 µg/h D-TRANS matrix system is bioequivalent to the 100 µg/h DURAGESIC fentanyl reservoir system.
- The pharmacokinetics of fentanyl does not change upon the repeated application of D-TRANS matrix system. Upon repeated application, there is ~40% accumulation of fentanyl exposures. Steady-state is most likely reached by the end of second consecutive dose.
- The systemic exposures (serum AUC and Cmax) of fentanyl after application of the
- D-TRANS matrix system increased in a dose proportional manner over the range of 25 µg/h to 100 µg/h.

- The D-TRANS matrix system is associated with less variability compared to DURAGESIC reservoir system and random spiking in serum fentanyl concentrations is not seen with D-TRANS matrix system over the range of 25 µg/h to 100 µg/h dose strengths.
- For the D-TRANS system, mean fentanyl C_{max} and AUC differed by less than 10% for the upper arm and upper back application sites. For the upper chest application, the mean C_{max} and AUC were 25% to 28% lower compared to the upper arm following single dose. With repeated application, the differences between the sites decreased.
- Fentanyl pharmacokinetic parameters were similar between the fair-skinned Caucasian and dark-skinned African descent groups aged 18 to 45 years.
- After a single application, the mean C_{max} was slightly lower in the elderly subjects (65 – 81 yrs) as compared to the corresponding values in the young adults (18 – 33 yrs). The AUC was found to be slightly higher in elderly with mean t_{1/2} approximately 10 hours longer in elderly subjects compared to young adults.
- The effect of heat is similar for both DURAGESIC and D-TRANS matrix system throughout the duration of the application. The initial application of heat (0 to 10 hours) significantly increased serum fentanyl concentrations for both DURAGESIC (C₁₀ and AUC₍₀₋₁₀₎ by 81% and 184%) and D-TRANS matrix system (C₁₀ and AUC₍₀₋₁₀₎ by 61% and 120%). The effect was comparatively minimal (less than 26 % for both formulations) with the second application of heat between 26 – 36 h.
- The D-TRANS matrix has a better adhesion compared to Duragesic over the duration of the 72-hr wearing period. Further the adhesion characteristics are not significantly affected by repeated application, heat and skin type by African descent or geriatrics.
- In all the clinical pharmacology and biopharmaceutical studies, a sensitive, precise and accurate LC-MS/MS bioanalytical method was employed for measuring serum fentanyl concentrations.

2 Question-Based Review (QBR)

2.1 General Attributes

DURAGESIC is a transdermal fentanyl reservoir system that is currently approved (in 1990) and marketed in the United States. It is indicated for the management of persistent, moderate to severe chronic pain that:

- Requires continuous, round-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.

DURAGESIC should be used only in patients, who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose that is at least equivalent to DURAGESIC 25 µg/h. The transdermal reservoir system is a form, fill and seal patch construction with a fentanyl gel as the drug reservoir component and is available in 5 dosage strengths of 12.5, 25, 50, 75 and 100 µg/h.

In 2005, FDA issued an alert for “Narcotic Overdose and Death” based on review of fatalities reported to the voluntary adverse event reporting system that were possibly due to the unintentional overdose of fentanyl transdermal patch. Factors identified as possibly related to unintentional overdose included: use of high doses of the fentanyl patch and/or multiple patches (sometimes in combination with other drugs), possible medication errors, accidental exposure (e.g., coming in contact with a discarded patch), application of a heat source to the patch possibly resulting in increased fentanyl absorption, injection or ingestion of the patch contents, and suspected transdermal patch malfunction (e.g., leaking patches). In addition, several patients reported poor adhesion of the patches to the skin. The DURAGESIC product label addresses issues regarding proper use of the product (e.g., risk of abuse and diversion, avoidance of direct heat sources to the patch, proper disposal of a discarded patch).

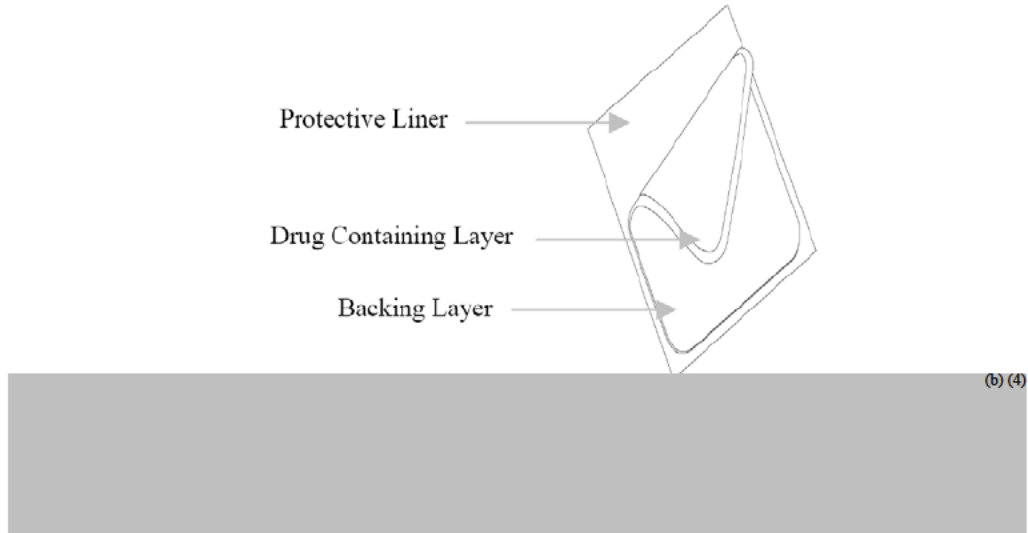
Despite these efforts, there were continued reports of death and life-threatening adverse events related to fentanyl overdose. This prompted FDA to issue another alert in 2007 updating the information regarding appropriate prescribing, dose selection and safe use of fentanyl transdermal system.

In an attempt to overcome the possibility of fentanyl gel leakage as well as increase the skin adhereability, the sponsor developed a D-TRANS fentanyl matrix system (herein after referred to as “D-TRANS” matrix system for all the 5 strengths. This product is currently marketed outside the US under the international trade name DUROGESIC since 2004 and was found to be bioequivalent to the ex-US reservoir system.

In the current submission, the sponsor is seeking approval of a revised formulation (D-TRANS matrix system) for transdermal delivery of fentanyl in the US. Supporting the new matrix formulation from clinical pharmacology perspective is a pivotal bioequivalence (BE) study (FEN-PAI-1019) assessing the D-TRANS matrix system to DURAGESIC for the highest strength of 100 µg/h in healthy subjects. Other clinical pharmacology information are provided from 4 studies (C-2002-047, C-2002-048, C-2002-052), and C-2004-005) evaluating the pharmacokinetics of fentanyl after single and repeated applications, dose proportionality, the pharmacokinetics in different age groups and skin types, and the effects of external heat. Two studies (C-2002-050 and C-2002-053) were conducted to assess the contact skin sensitization potential and the phototoxicity potential of the D-TRANS matrix system. Further, 3 studies (C-2003-038, C-2002-046 and C-2002-049) assessing the BE of the D-TRANS matrix system with the international reservoir system DUROGESIC were also used in support of seeking approval. No new clinical safety and efficacy study was conducted for this submission.

2.1.1 What are the highlights of the D-TRANS matrix system as they relate to clinical pharmacology review?

The D-TRANS matrix system is a multi-laminate product comprised of two functional layers: a single layer of fentanyl containing pressure-sensitive acrylate adhesive and the backing film. This design replaces the reservoir gel, rate-control membrane, and separate adhesive layer found in the reservoir system. The skin stratum corneum provides the drug delivery rate-control in the D-TRANS matrix system. Further, the need for fentanyl release equilibration caused by diffusion in the reservoir system is eliminated. A schematic of the D-Trans matrix system is presented below:



Source: Figure 2 of the Sponsor Report introduction.pdf

Figure 1: Schematic of D-TRANS Fentanyl Matrix System

The D-TRANS matrix system has (b) (4) that is removed and discarded before the patch is applied to the skin. An S-cut slit in the protective liner to facilitate removal of the liner by the patient.

2.1.2 What is the composition of to-be-marketed formulation of D-TRANS matrix system?

Fentanyl the active ingredient represents (b) (4), while the polyacrylate adhesive represents (b) (4) of the total weight of the patch (without the protective liner) respectively. The rest of the weight of the D-TRANS matrix system is represented by the backing layer (b) (4). The adhesive side of the patch is covered by an oversized, slit protective liner that is removed before use. The various strengths of the D-TRANS matrix system (without the protective liner) are compositionally proportional as different strengths represent different surface areas. The detailed quantitative composition is presented in the table below in Table 1:

Table 1: Quantitative composition of D-TRANS Fentanyl matrix system

Quantity Per Patch (mg per patch)					
Nominal Delivery Rate:		12 µg/h	25 µg/h	50 µg/h	75 µg/h
Patch Area (cm²):		5.25	10.5	21.0	31.5
Quality Standard		42.0			
Components	Function				
Backing Layer ^a					
Drug Reservoir					
Protective Liner ^a					
Inks					
Total Patch Weight					
PATCH WEIGHT WITHOUT PROTECTIVE LINER					

^a Weights shown are examples. Material added to batch as (b) (4)

^b Dry weight

^c (b) (4)

^d (b) (4)

^e (b) (4)

^f (b) (4)

^g (b) (4)

Source: Table 1 of the Sponsor Report description-and-composition-alza.pdf

Note: Lowest strength is referred to as 12 µg/h even though it is exactly half of 25 µg/h (12.5 µg/h) to avoid prescription confusions with (b) (4) µg/h.

2.2 General Clinical Pharmacology

2.2.1 What are the design feature of the clinical pharmacology and clinical studies used to support dosing or claims?

- Single dose, multiple dose pharmacokinetics and the dose-proportionality assessment were characterized in cross-over studies. Dose-proportionality was assessed over 25 -100 µg/h. The single dose/multiple dose PK study also assessed the effect of site (outer arm, upper back and upper chest) on the pharmacokinetics for both the formulations.
- The effect of heat was assessed for both D-TRANS matrix system as well as DURAGESIC at a single dose of 25 µg/h in a cross-over fashion. Heat was applied over two intervals of 0 – 10 h and 26 – 36 h.
- The effect of skin-type and age were assessed in a single dose study with D-TRANS matrix system (100 µg/h) in fair-skinned Caucasians, dark-skinned subjects of African descent and fair-skinned Caucasians 65 – 81 years old.

2.2.2 What are the the PK characteristics of the drug and/or its metabolite?

DURAGESIC, transdermal reservoir system is already approved and the pharmacokinetics of fentanyl has already been characterized. This section will present the PK characterization of fentanyl when administered as D-TRANS matrix system.

2.2.2.1 What are the single dose and multiple dose PK parameters?

Study C-2002-047, an open-label, single-center, 2-treatment, 2-period, sequential design study was designed to characterize fentanyl pharmacokinetics following single and repeated applications of D-TRANS matrix system (100 µg/h). Subjects received a single-application of the D-TRANS fentanyl matrix system 100 µg/h, in Period 1, which was worn for 72 hours and repeated-applications of the D-TRANS fentanyl matrix system 100 µg/h, 4 consecutive applications in Period 2, each worn for 72 hours (total wearing period of 288 hours). The time course of serum fentanyl is shown in Figure 2.

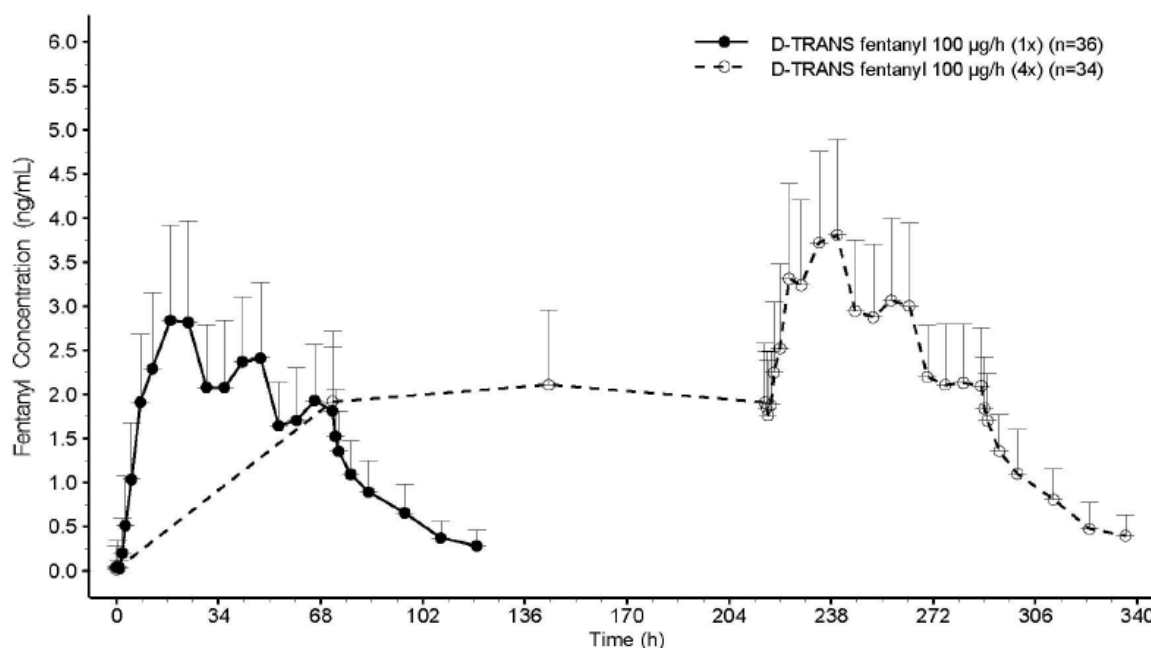


Figure 2 Mean (SD) serum fentanyl concentration-time profiles following single and repeated applications of D-TRANS 100 µg/h in healthy adult subjects

Source: Figure 11.2.1 of sponsor report c-2002-047.pdf

It can be clearly seen that there is accumulation following repeated applications and that steady-state is probably achieved by the end of second consecutive 72 h system application. Comparison of the PK following the 4th application and the single dose suggest ~40% accumulation with repeated dose. Also it can be seen from the Table below, the pharmacokinetics of fentanyl do not change with repeat application.

Table 2 Mean (SD) serum fentanyl PK parameters following single and repeated application of D-TRANS matrix system in healthy adult subjects.

Parameter	D-TRANS Fentanyl 100 µg/h, Single Application (n=33) ^b	D-TRANS Fentanyl 100 µg/h, Repeated Applications ^a (n=33) ^b
C _{max} (ng/mL)	3.15 (1.08)	4.20 (1.16)
t _{max} (h)	23.6 (10.4)	19.7 (9.1)
AUC ₍₀₋₇₂₎ (ng.h/mL)	144 (43)	NA
AUC _t (ng.h/mL)	177 (52.6)	NA
AUC ₍₀₋₁₂₀₎ (ng.h/mL)	177 (52.5)	NA
AUC _∞ (ng.h/mL)	185 (55.8)	NA
AUC ₍₂₁₆₋₂₈₈₎ (ng.h/mL)	NA	204 (52.8)
t _{1/2} (h) ^c	19.9 (5.8)	23.5 (7.2) ^d

^a Pharmacokinetic parameters were determined following the 4th application

^b Excluding 3 subjects (premature terminations from the study)

^c Terminal half-life was determined after the system was removed.

^d n=32

Source: Table 4 of the sponsor summary-clin-pharm.pdf

2.2.2.2 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose-proportionality was assessed in Study C-2002-048 over the dose strengths of 25 µg/h to 100 µg/h. It can be clearly seen from the Figure 3, the pharmacokinetics of fentanyl are dose proportional over the dose range studied.

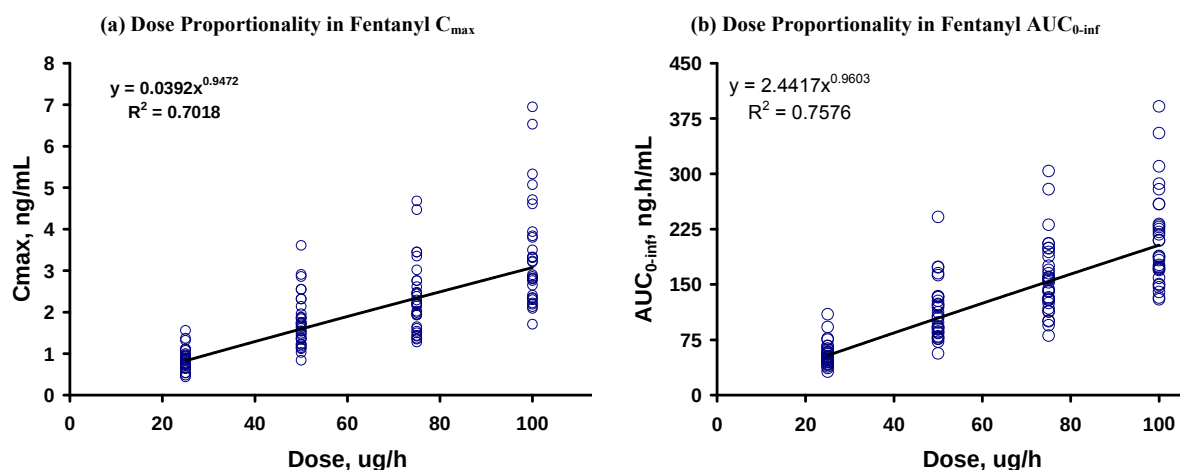


Figure 3 Dose Proportional Increase in Fentanyl C_{max} and AUC_{0-inf} when administered as D-TRANS matrix system

2.2.2.3 What is the variability in the time-course of serum fentanyl when applied as D-TRANS matrix system?

With the DURAGESIC reservoir system and other fentanyl transdermal products, random spikes of unexpectedly high concentrations were seen in the databases available to the Agency and has been a topic of interest from a safety point of view. Investigation into whether these spikes are because of sampling errors or if they are real is ongoing. Since all the clinical pharmacology and biopharmaceutics studies were performed in healthy subjects under continuous naltraxone block, the opioid effects due to random spiking if any would not be detected. Hence the individual time-courses following application of D-TRANS matrix systems were plotted for all dose strengths from all the studies to explore for random spikes in fentanyl serum concentration. The threshold to categorize whether an observed concentration is part of the natural time course profile or if it was a spike was any concentration that is higher than thrice the mean C_{max} value at that dose level. This threshold value is the same as that used previously to assess this phenomenon. In **Figure 4**, data from the pivotal BE study FEN-PAI-1019 is shown and it can be seen that the D-TRANS matrix system is associated with less variability in general compared to DURAGESIC reservoir system and random spiking in serum fentanyl concentrations is not associated with D-TRANS matrix system in this study or any of the other pharmacokinetics studies submitted for the current sNDA application. Serum fentanyl time-courses for all the studies are provided in the **Appendix 4.1**.

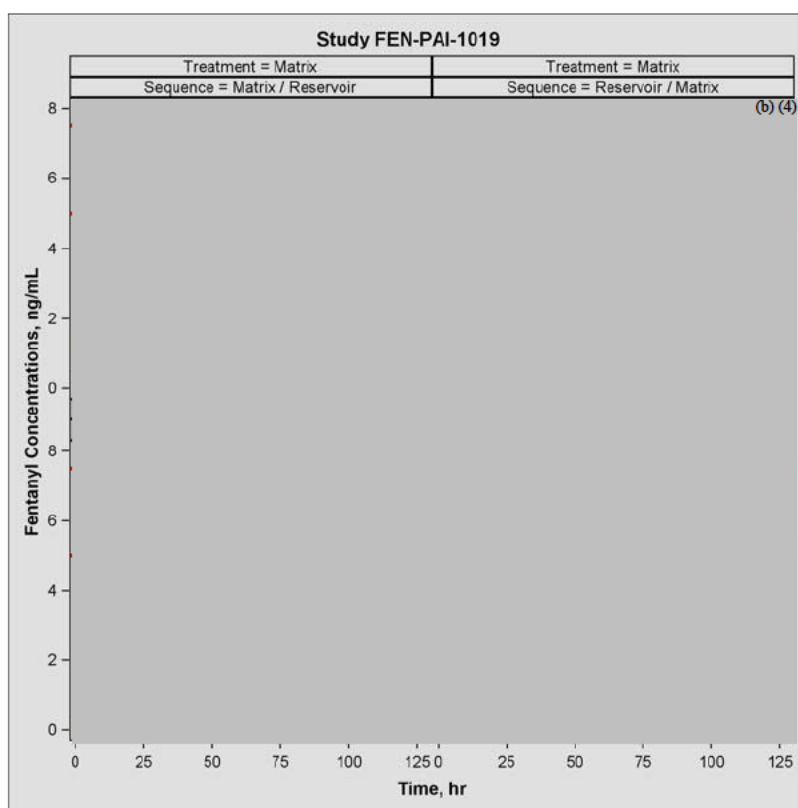


Figure 4: No evidence of random spiking in the serum fentanyl concentration following application of D-TRANS matrix system and less between subject variability compared to DURAGESIC

2.2.2.4 How does the system adherence of D-TRANS matrix compare with DURAGESIC reservoir?

The D-TRANS matrix in general had a greater percentage of subjects with $\geq 90\%$ adherence than the Duragesic system over the 72 hr wearing period as illustrated in the pivotal bioequivalence study (**Figure 5**). Also see for further plots in Appendix 4.2.

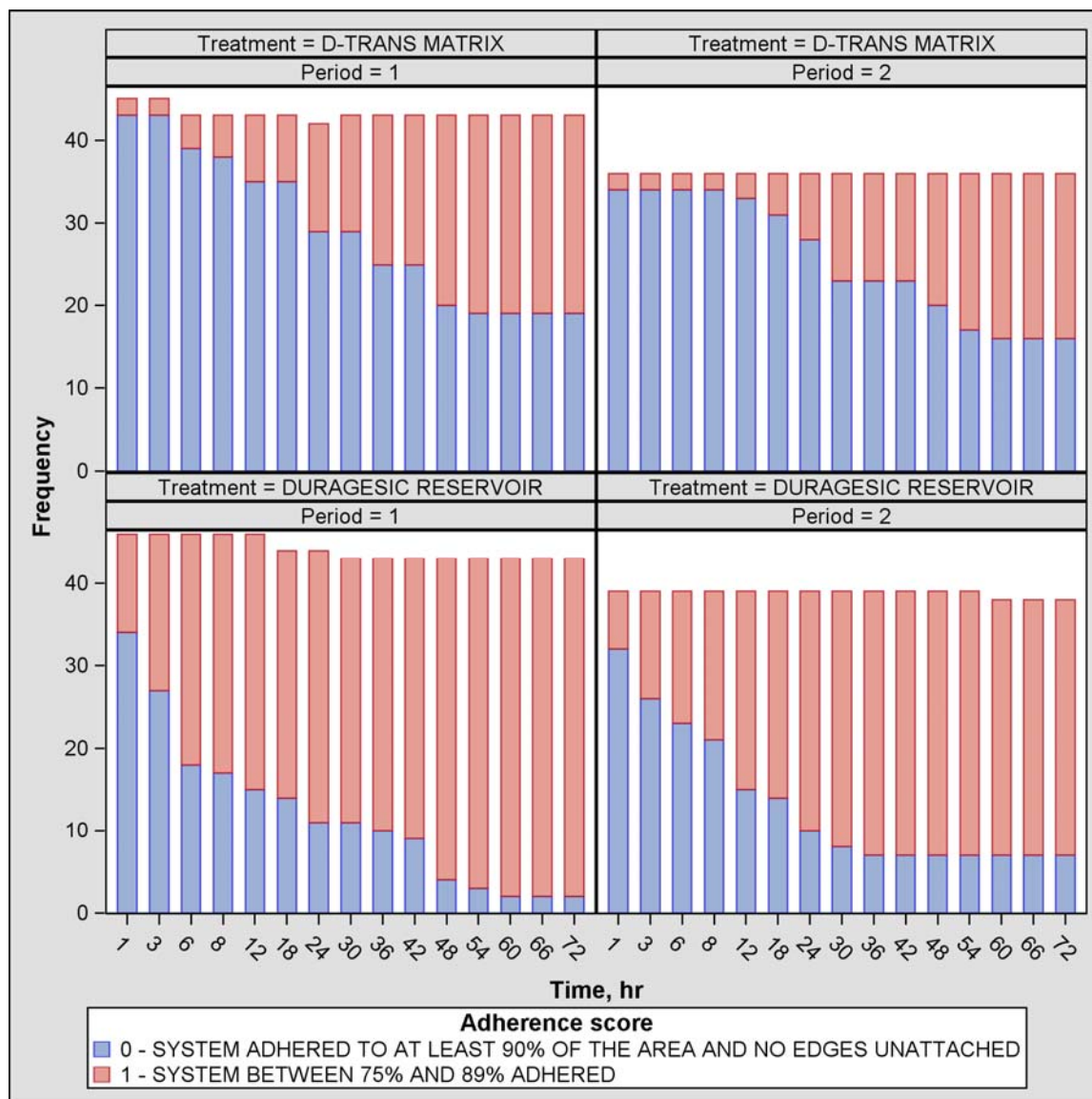


Figure 5: D-TRANS matrix formulation has better adherence than Duragesic reservoir formulation in the pivotal bioequivalence study.

Further upon repeated application there were no marked differences between the adhesion functionality over the duration of the 72 hr wearing time between the applications as seen in **Figure 6**.

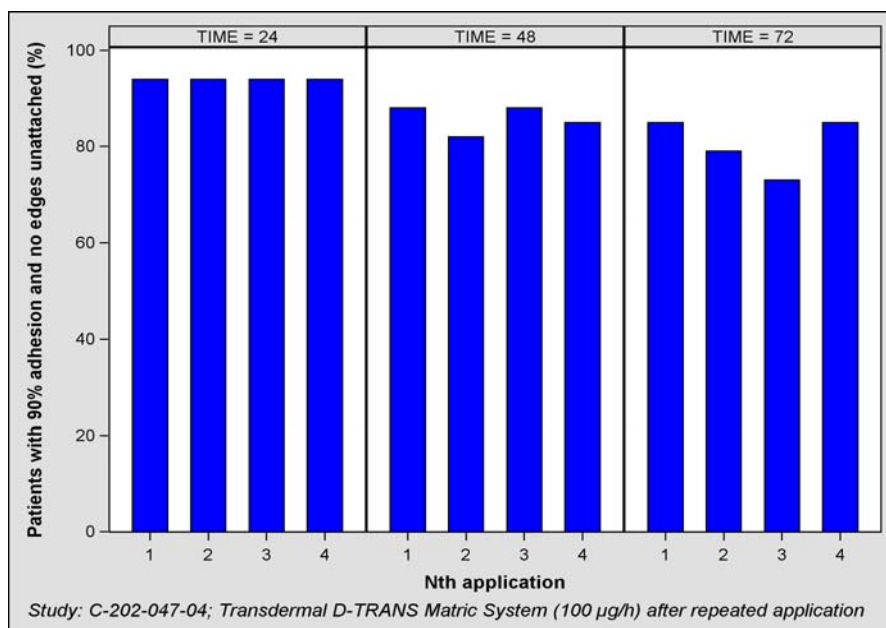


Figure 6: The adhesion characteristics following repeated applications are reasonably similar over the 72-hr wearing period per application.

Similarly a greater of D-TRANS matrix systems adhered to atleast 90% of the application-site area in the presence of heat compared to the Duragesic systems (**Figure 7**).

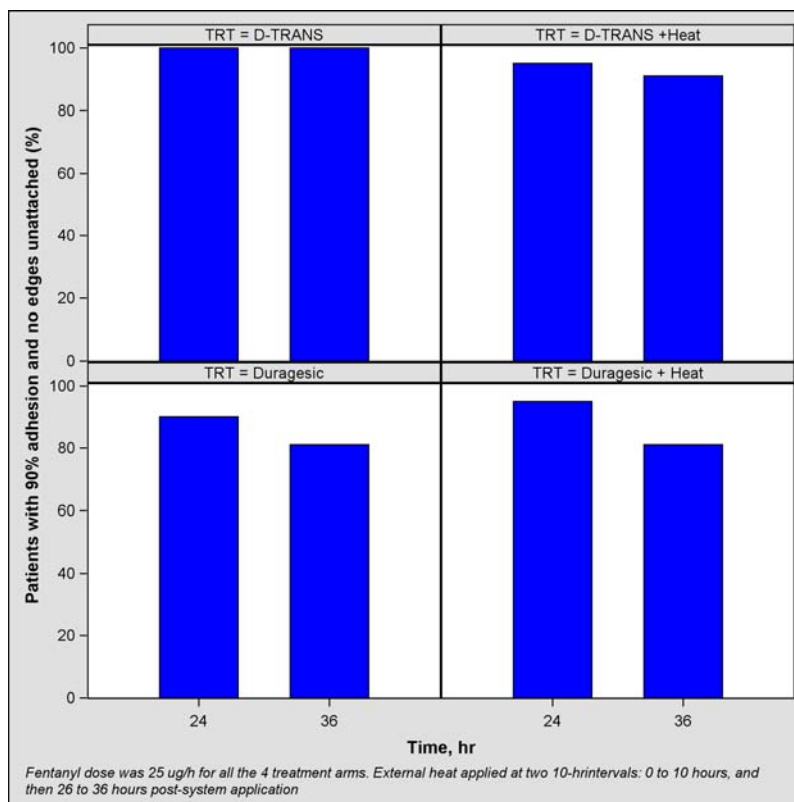


Figure 7: The adhesion of D-TRANS matrix is not significantly affected by heat and performs better than Duragesic system.

2.3 Intrinsic Factors

This section contains the assessment from newly conducted studies with D-TRANS matrix system formulation of the effects of site of application, skin-type, and age on the pharmacokinetics of fentanyl upon the application of D-TRANS matrix system.

Site of application:

As a part of the study C-2002-047, which was primarily aimed at characterizing the pharmacokinetics following single and repeat application, the effect of site of application was also explored. In this study, subjects were randomized to receive the D-TRANS fentanyl systems on the upper outer arm, upper chest or upper back. It can be seen from Figure 4 the fentanyl exposures achieved upon application to the chest are lower compared to upper back and upper outer arm for both single and repeat applications.

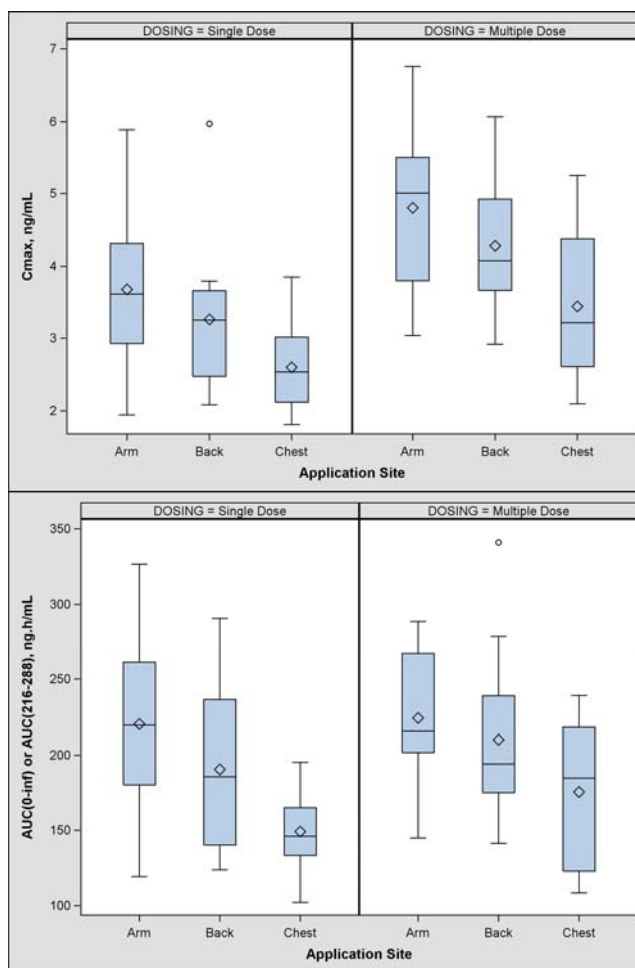


Figure 8: Fentanyl Serum Exposures following application of D-TRANS matrix system at different sites (Top: for C_{max}; Bottom: for AUC [Note: AUC (0 – inf) for Sing Dose and AUC (216 – 288) for Multiple Dose])

However, upon repeated application, the differences are slightly lower. During the single-application treatment, the mean AUC_{inf} values for the upper back and upper chest were 10% and 29% lower, respectively, than the AUC_{inf} for the upper outer arm. During the repeated-applications treatment, the mean AUC_{inf} values for the upper back and upper chest were 6% and

22% lower, respectively, than the AUC_{inf} for the upper outer arm. Since the exposures differences are less than 30% and show a trend towards decreased application site differences with repeated application, no new specific recommendation for the site of application are deemed necessary.

Effect of Skin-type

The pharmacokinetics of fentanyl following application of a single dose (100 µg/h) of D-TRANS matrix system to fair-skinned Caucasians and dark-skinned subjects of African descent was characterized in Study C-2002-052. Fentanyl pharmacokinetic parameters were similar between the fair-skinned Caucasian and dark-skinned African descent groups aged 18 to 45 years as seen in **Figure 9**.

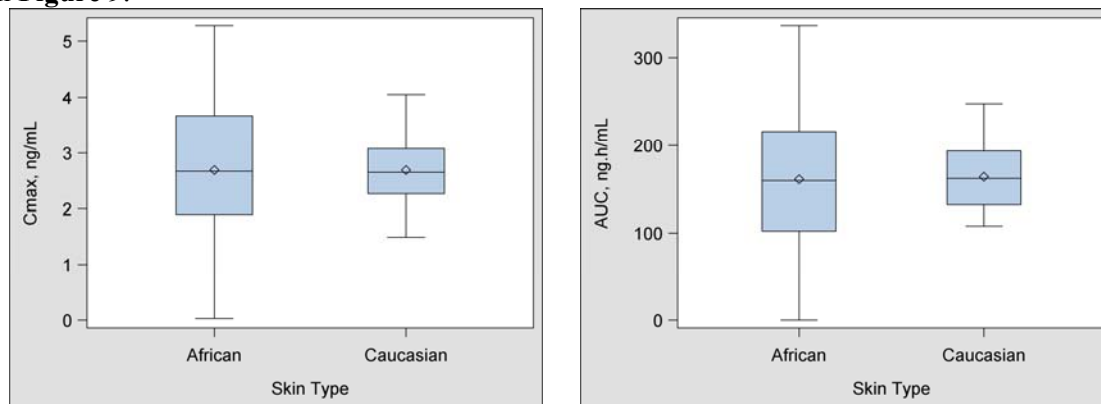


Figure 9: Fentanyl pharmacokinetics when applied as D-TRANS matrix system are similar between fair skinned Caucasian and dark skinned African descent subjects (Left: for C_{max}; Right: for AUC)

Effect of Age:

The effect of age in healthy Caucasian subjects was assessed along with the effect of skin type in Study C-2002-052. After a single application of D-TRANS 100 µg/h, the mean C_{max} was slightly lower in the elderly Caucasian subjects (65 – 81 yrs) as compared to the corresponding values in the young adult Caucasians (18 – 33 yrs). However, the AUC was found to be slightly higher in elderly Caucasians. The mean t_{1/2} was found to be approximately 10 hours longer in elderly Caucasian subjects than in the young adult Caucasian subjects. Further, it must be noted that the between subject was higher in elderly subjects compared to young adults and the exposure ranges are overlapping.

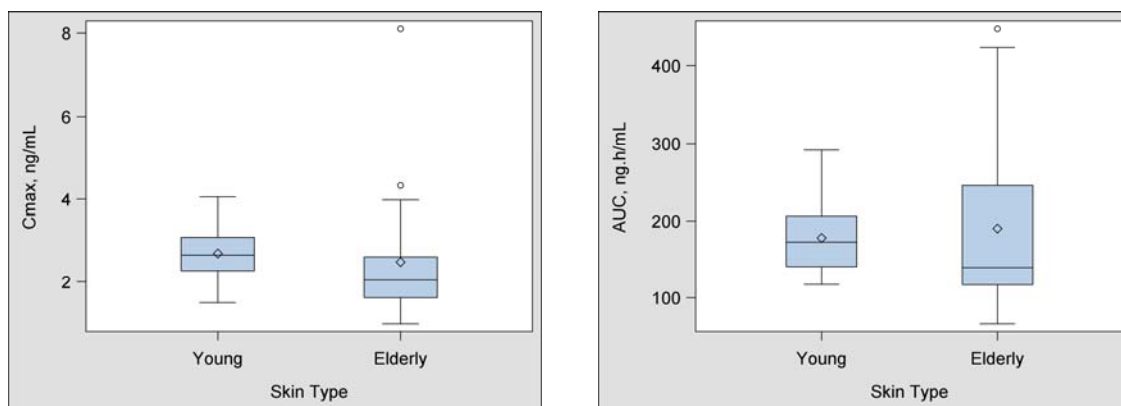


Figure 10: Fentanyl pharmacokinetics when applied as D-TRANS matrix system are similar between young Caucasians (18 – 33 yrs) and elderly Caucasian subjects (65 – 81 yrs) (Left: for C_{max}; Right: for AUC)

2.4 Extrinsic Factors

In this section only the effect of application of external heat on the pharmacokinetics of DURAGESIC and D-TRANS matrix system will be discussed.

Effect of external heat:

The effects of external heat on serum fentanyl concentrations following the application of a DURAGESIC (25 µg/h) and a D-TRANS matrix system (25 µg/h system) was evaluated in Study C- 2004-005. External heat with a standardized heating pad was applied at two 10-hour intervals: 0 to 10 hours, and then 26 to 36 hours post system application. Each transdermal system was worn for 36 h only. It can be clearly seen from the Figure 11 below the effect of heat is similar for both DURAGESIC and D-TRANS matrix system throughout the duration of the application.

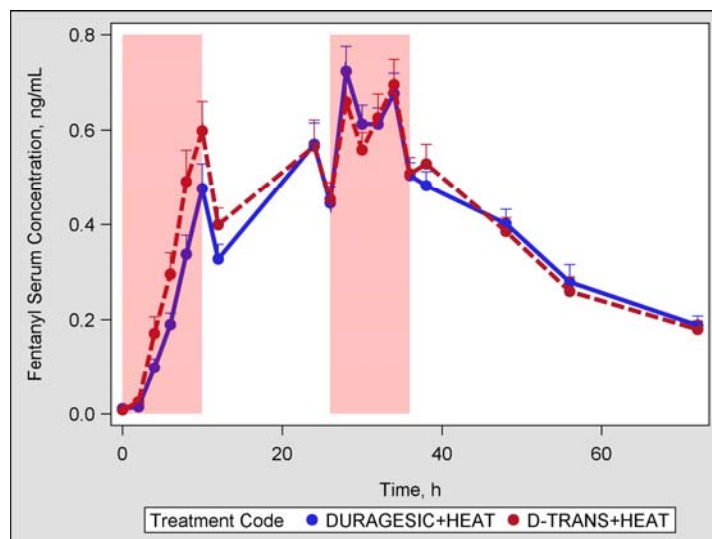


Figure 11: The time-course of fentanyl is similar following application of external heat for DURAGESIC and D-TRANS matrix system (25 ug/h) (Error bars represent Standard Error. The red bands represent the duration of heat application)

The initial application of heat (0 to 10 hours) significantly increased serum fentanyl concentrations for both DURAGESIC and D-TRANS matrix system formulations as seen in

Figure 12. However, the effect was comparatively minimal with the second application of heat between 26 – 36 h. Further the effect of heat is lower on D-TRANS matrix system compared to that on DURAGESIC.

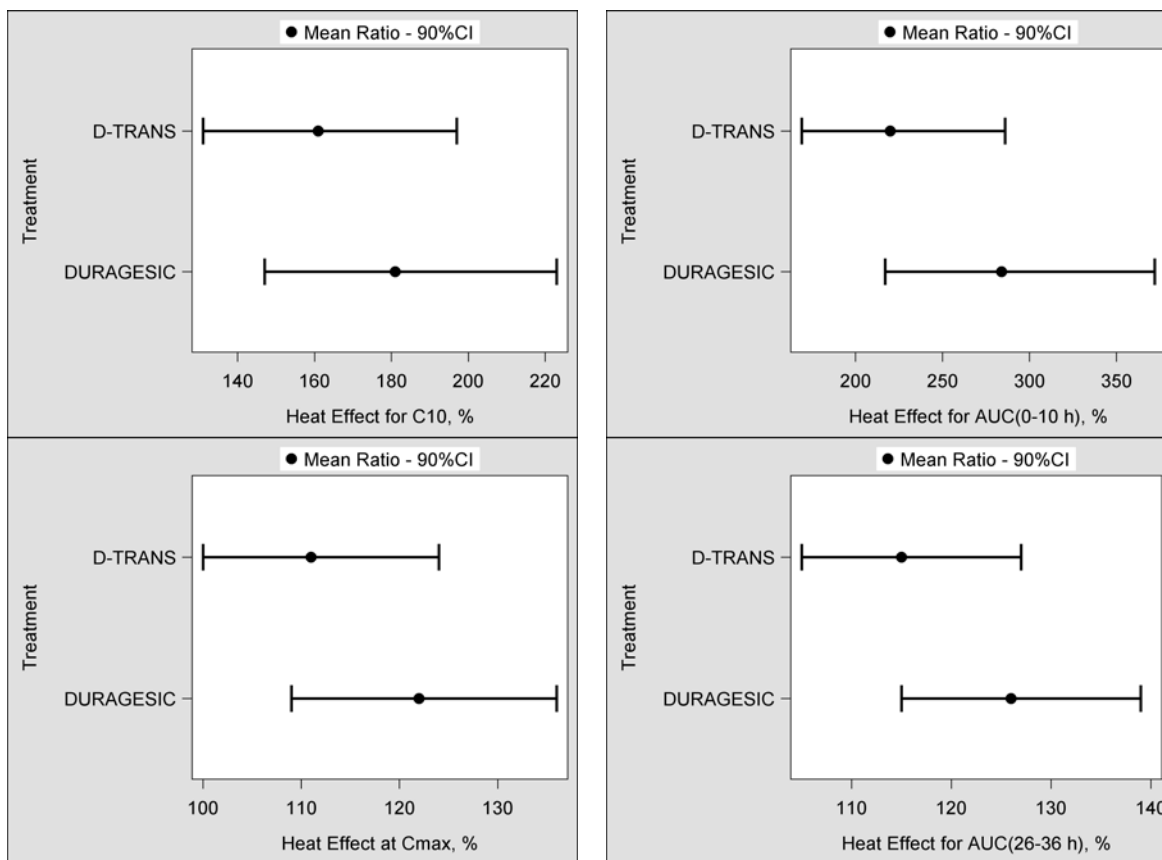


Figure 12: Application of heat increases the exposure of serum fentanyl for both DURAGESIC and D-TRANS matrix system (Top: For initial heat application, Bottom: For second heat application)

Further, over the entire duration of the treatment there was no significant difference in the exposure of fentanyl with or without application of heat (AUC_{0-inf} : 103 (94 – 112)).

2.5 General Biopharmaceutics

2.5.1 If altered approved products were used as active controls, how is BE to approved product demonstrated?

The current approved transdermal system is DURAGESIC reservoir system, a form-fill-seal design containing fentanyl and alcohol gelled in a drug reservoir that delivers fentanyl continuously to the skin via a rate-controlling membrane during the 72-hour application period. In the current submission, the sponsor is seeking for approval D-TRANS matrix system, a simple drug-in-adhesive-matrix, which if approved is intended to replace the DURAGESIC reservoir system. A pivotal single-dose BE study (Study FEN-PAI-1019) was designed to demonstrate BE between these two formulations at the highest strength 100 µg/h. The results of this study serve as the primary basis for the approval of D-TRANS matrix system.

The mean fentanyl serum concentration-time profiles following the administration of both D-TRANS matrix system and DURAGESIC indicate that the mean concentrations following the administration of the D-TRANS matrix system were greater during the first 24 hours of

application in comparison to that observed with the DURAGESIC. These differences decrease with time and become similar as seen in **Figure 13**.

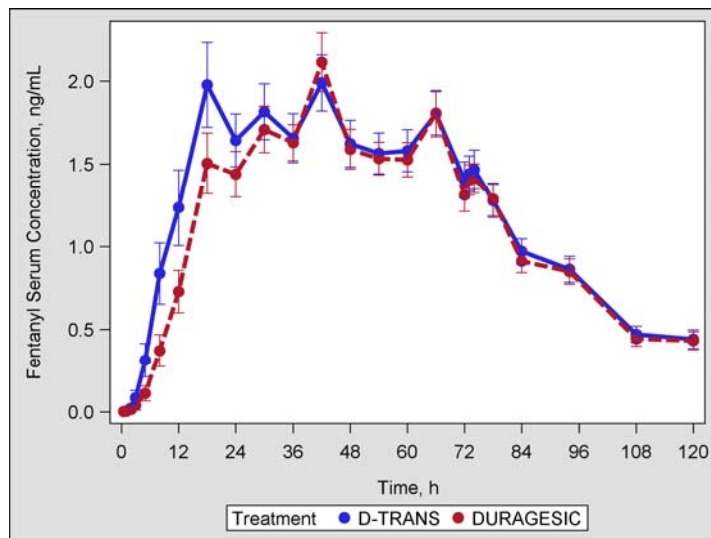


Figure 13: Mean serum concentration time profiles of fentanyl following administration of DURAGESIC and D-TRANS matrix 100 ug/h systems (The error bars represent 95% CI around the mean)

Statistical comparison shows the 90% CIs of the ratios of the geometric means for all fentanyl pharmacokinetic parameters were contained within the bioequivalence criteria of 80% to 125% as shown in **Figure 14**.

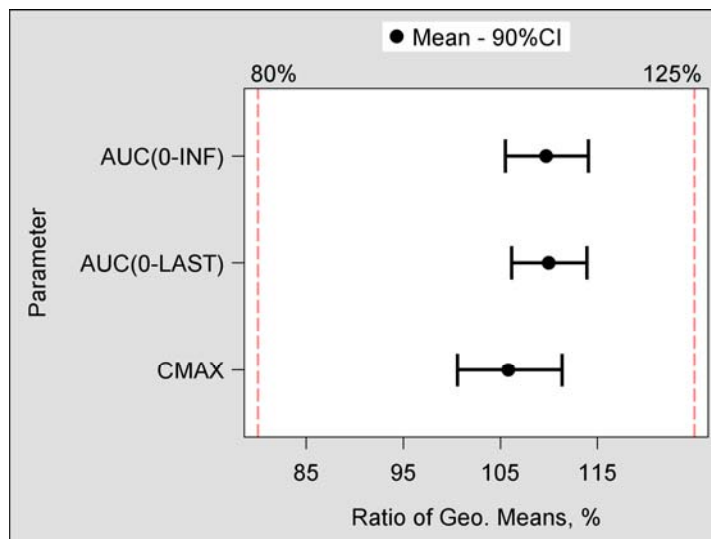


Figure 14: DURAGESIC (100 ug/h) and D-TRANS matrix systems (100 ug/h) are bioequivalent (Error bars represent 90% CI. The red dashed line represents the 80 – 125 % interval)

Additionally 3 more studies were conducted by the sponsor providing supporting BE information. These studies were aimed to support filing of the D_TRANS matrix system in the European Union. As such the reference product was the EU approved DUROGESIC reservoir product. The EU DUROGESIC reservoir system, is reported to be compositional different compared to

DURAGESIC. Since the composition of DUROGESIC is unknown, these additional studies were not reviewed.

2.6 Analytical

2.6.1 Is the bioanalytical method for serum fentanyl appropriately validated?

An LC-MS/MS method was developed and validated for the quantification of fentanyl in human serum. Internal standard (b) (4) was added and extracted along with the analyte using liquid/liquid extraction under basic conditions. Serum extracts were (b) (4) in an appropriate solvent before injection onto the LC-MS/MS. The PE Sciex API3000, PE Sciex API 365, and PE Sciex API III Plus series using an ESI interface were employed. Positive ions were monitored in the MRM mode.

The assay was validated in terms of recovery, linearity, accuracy, precision and sensitivity. The table below summarizes the results of the analytical method validation used for the clinical pharmacology studies.

Table 3: Summary of analytical method used for the clinical pharmacology studies

Parameter	Results
Linear Range	10 – 5000 pg/mL; LOQ = 10 pg/mL
Recovery	100 % over 10 – 5000 pg/mL in human serum; 95% for d ₅ -fentanyl in human serum
Inter-batch variation	Accuracy: (b) (4) Precision: (b) (4)
Intra-batch variation	Accuracy: (b) (4) Precision: (b) (4)
Bench-Top Stability (24 h at RT under white light)	99 % – 103 % as percent of Control
Freeze-Thaw Stability (5 cycles)	97 % – 105 % as percent Control
Long Term Stability (22 weeks at -20°C)	93 % – 94 % as percent Control
Reinjection of the extracted sample (for 6 days)	95 % – 101 % as percent Control
Refrigeration of the extracted sample (for 6 days, 2 h)	95 % – 101 % as percent Control
Selectivity	50% samples from 40 lots of human serum showed

Parameter	Results
	no interference at LLOQ (10 pg/mL). in the remaining samples the interference was less than 20% of the test LLOQ
Sensitivity	Lots within 20% of LLOQ and within 15 % of ULOQ (b) (4)

Note: Table constructed from sponsor report:mds-validation-report-for-fentanyl—project-18086-6.pdf

3 Labeling Comments

All the labeling modifications suggested by the sponsor pertaining to the clinical pharmacology sections are acceptable.

4 Appendix

4.1 Time course of Fentanyl in all the Clinical Pharmacology and Biopharmaceutics Studies submitted in the current submission

Figure 15: Study C-2003-038-00

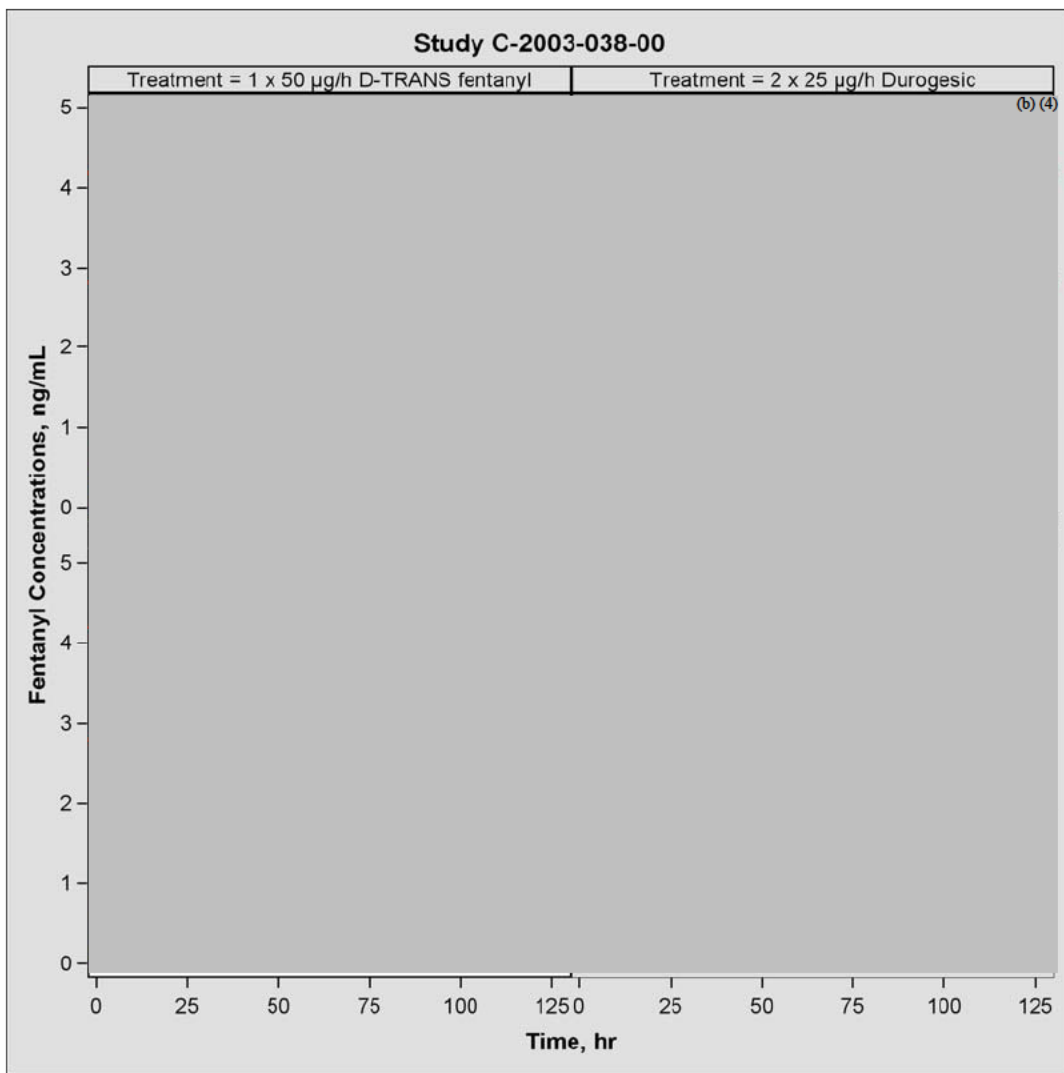


Figure 16: Study C-2002-049-00

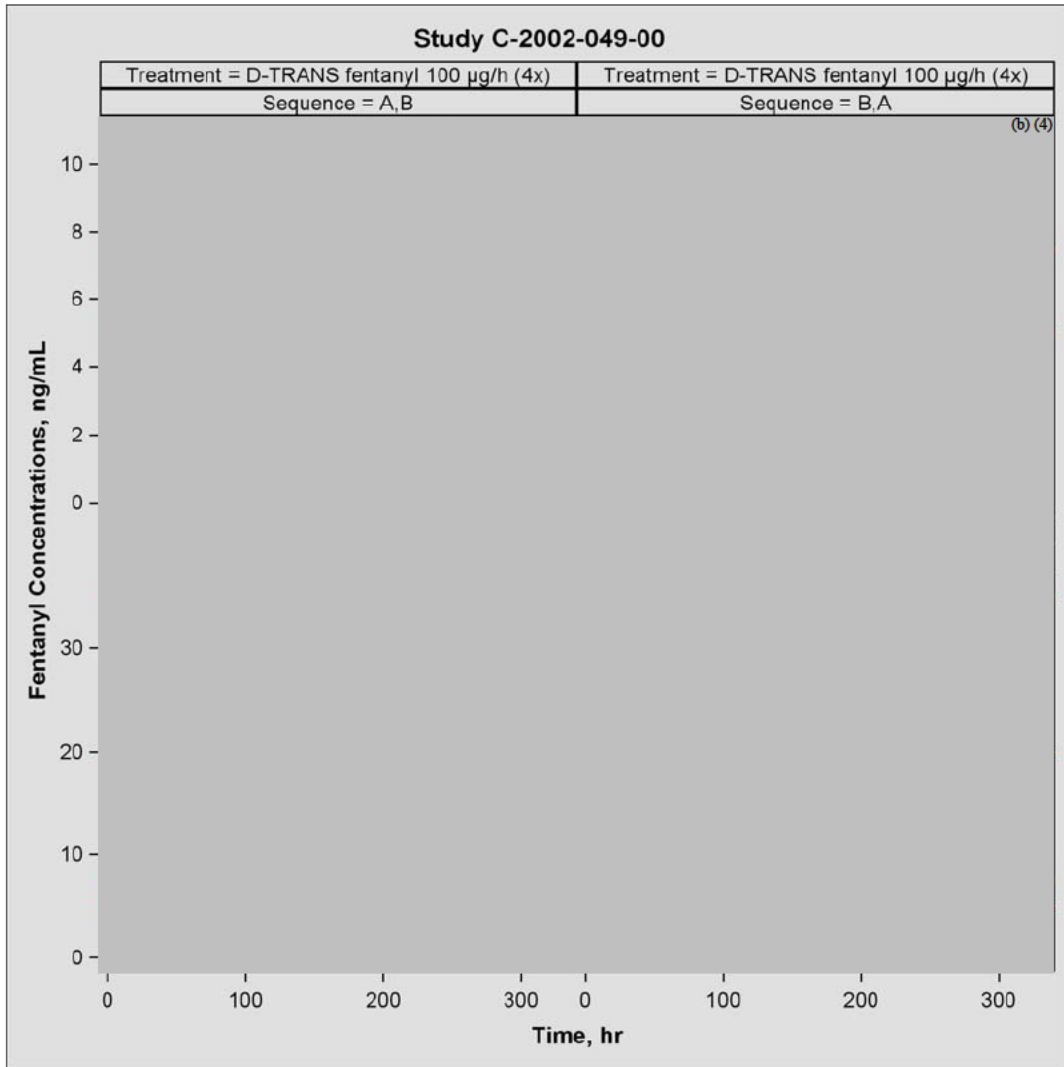


Figure 17: Study C-2002-046-00

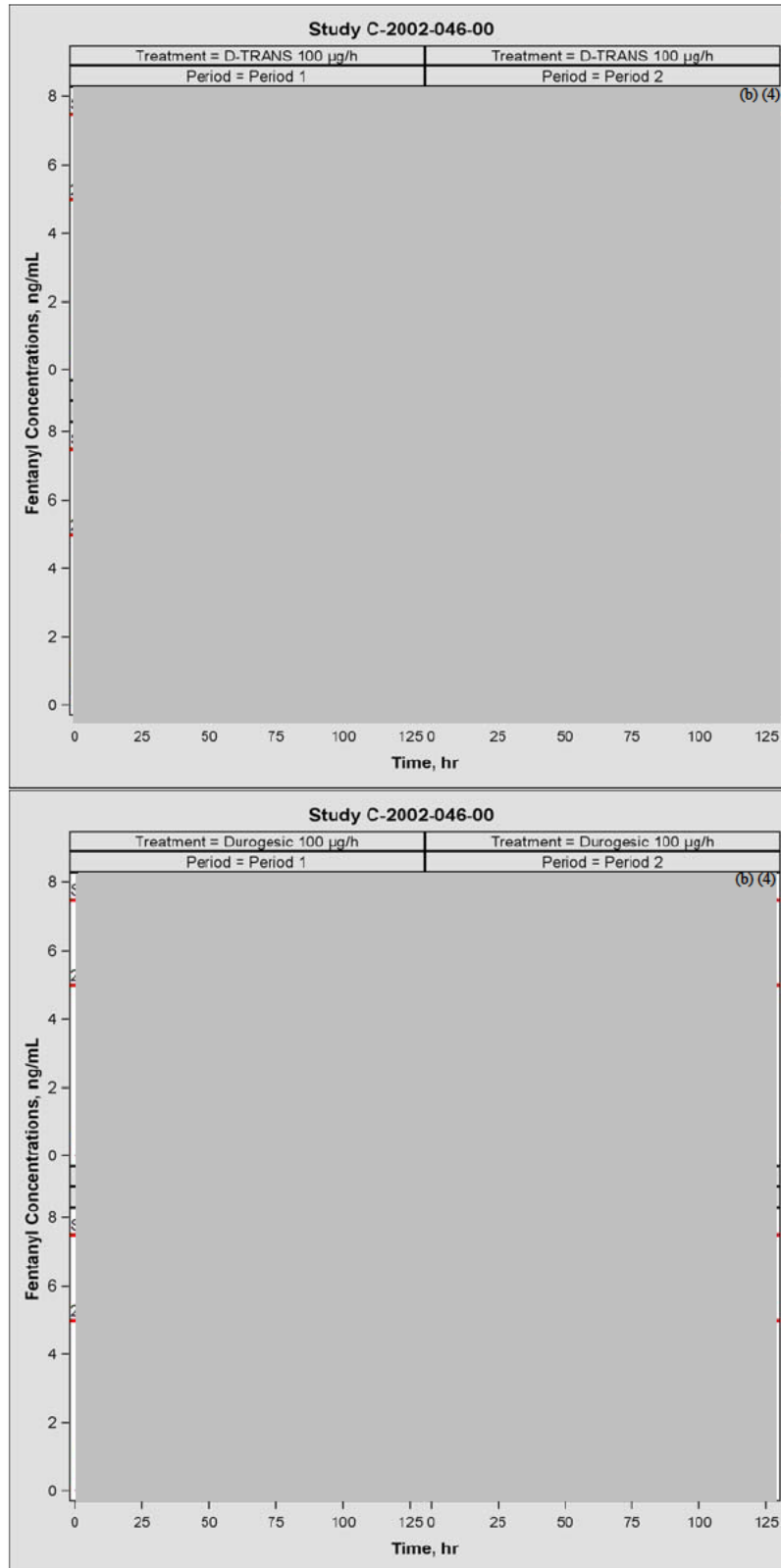


Figure 18: Study C-2002-047-00

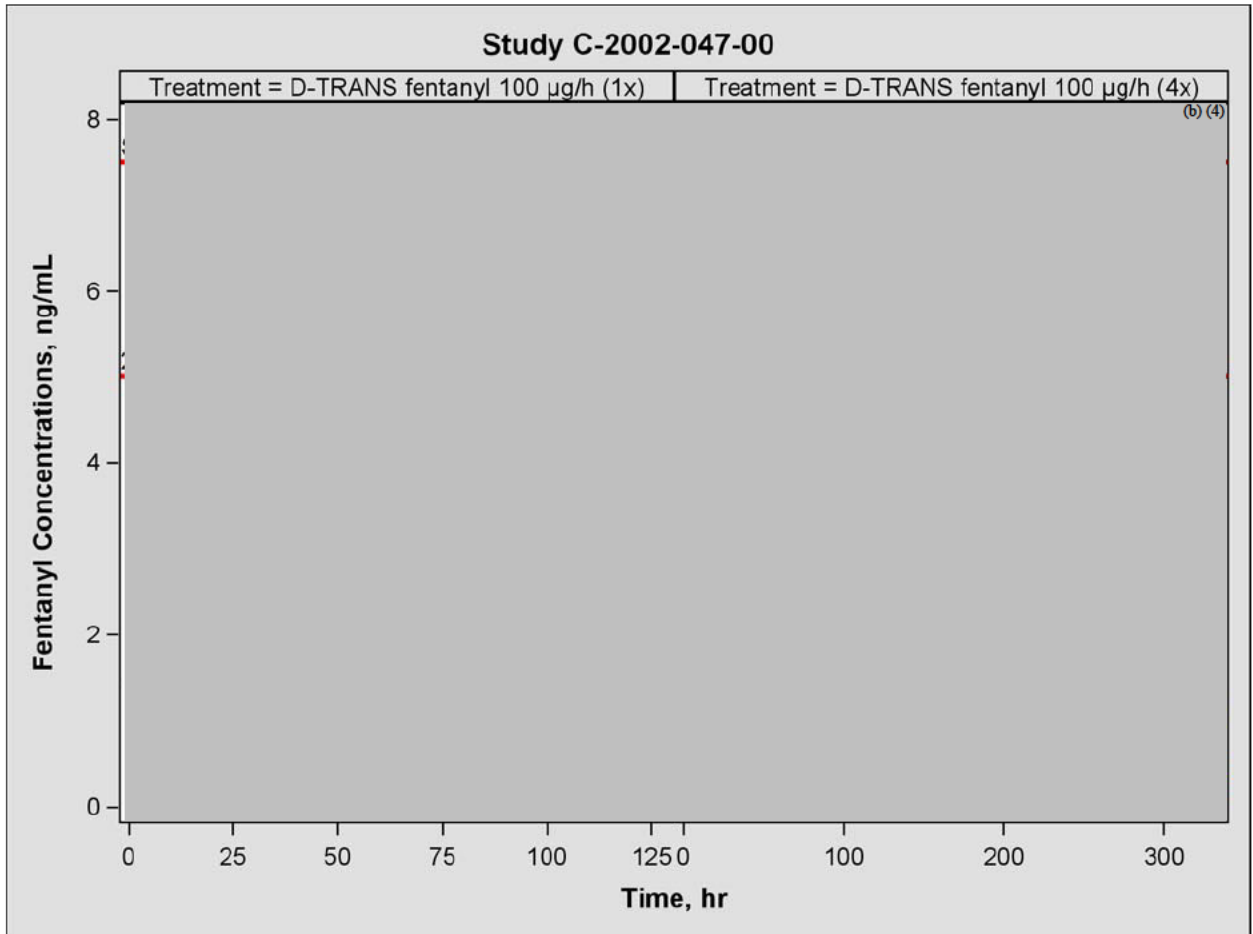
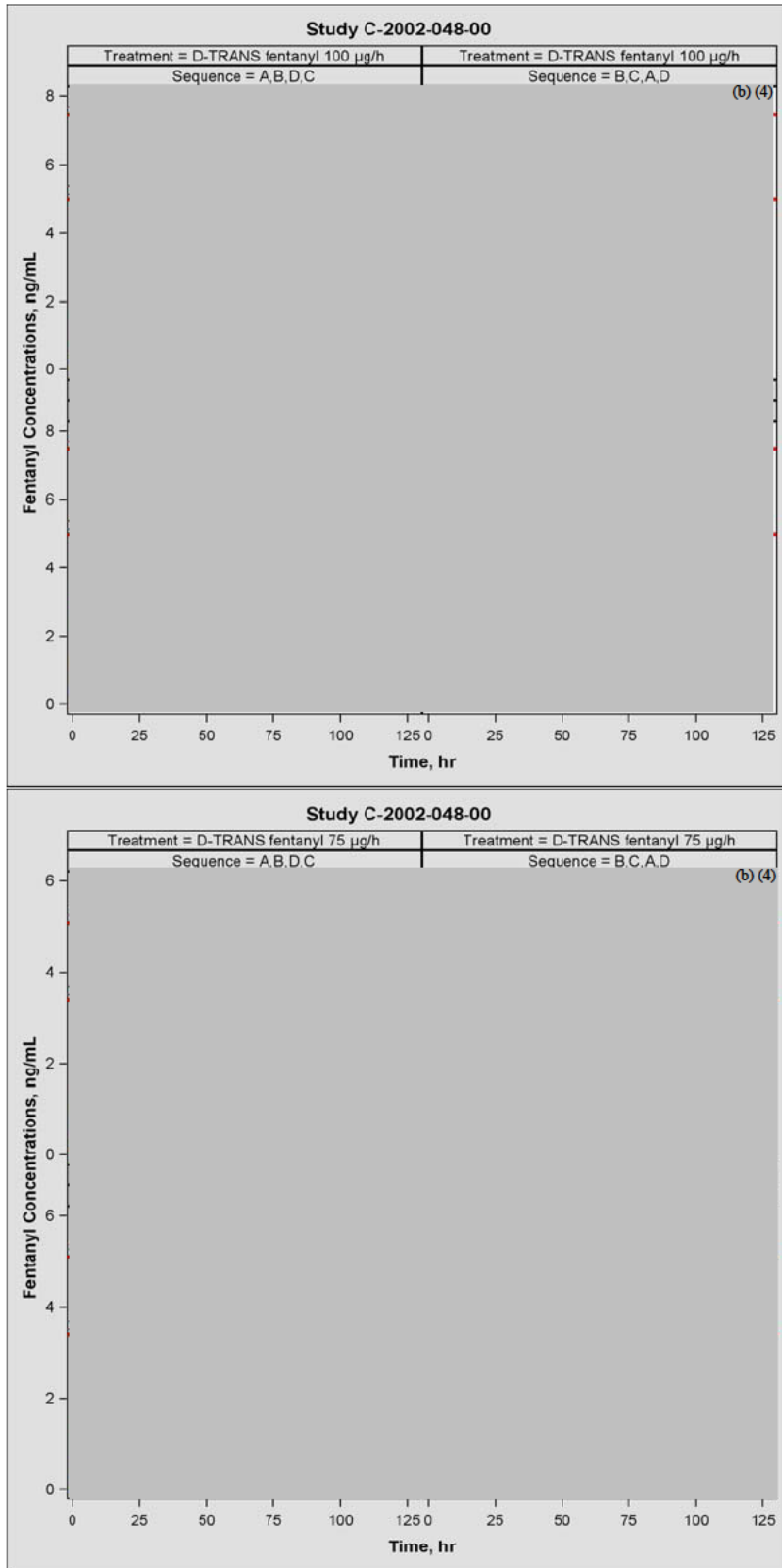


Figure 19: Study C-2002-048-00



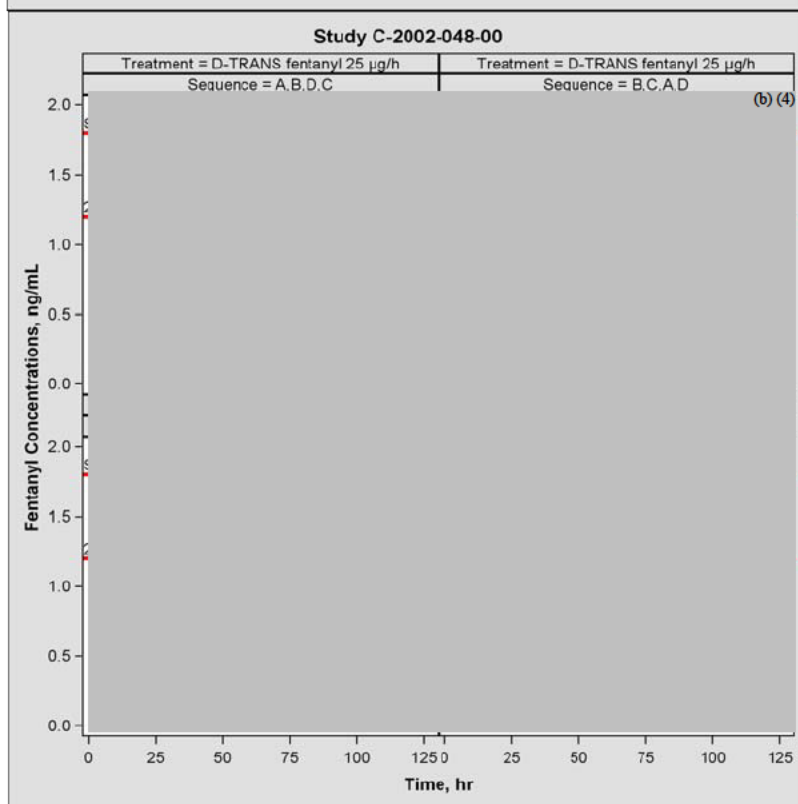
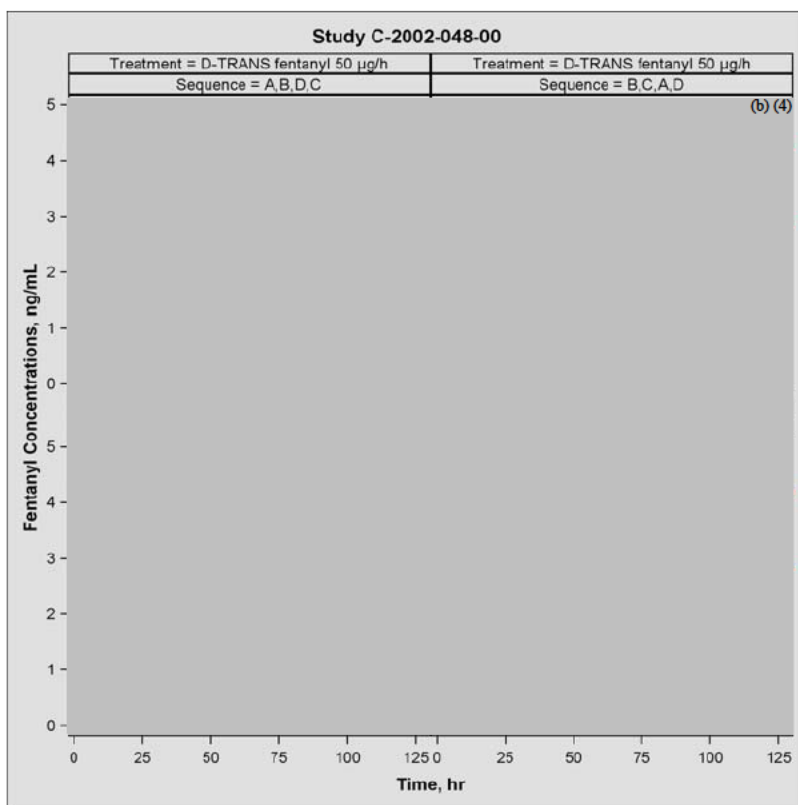
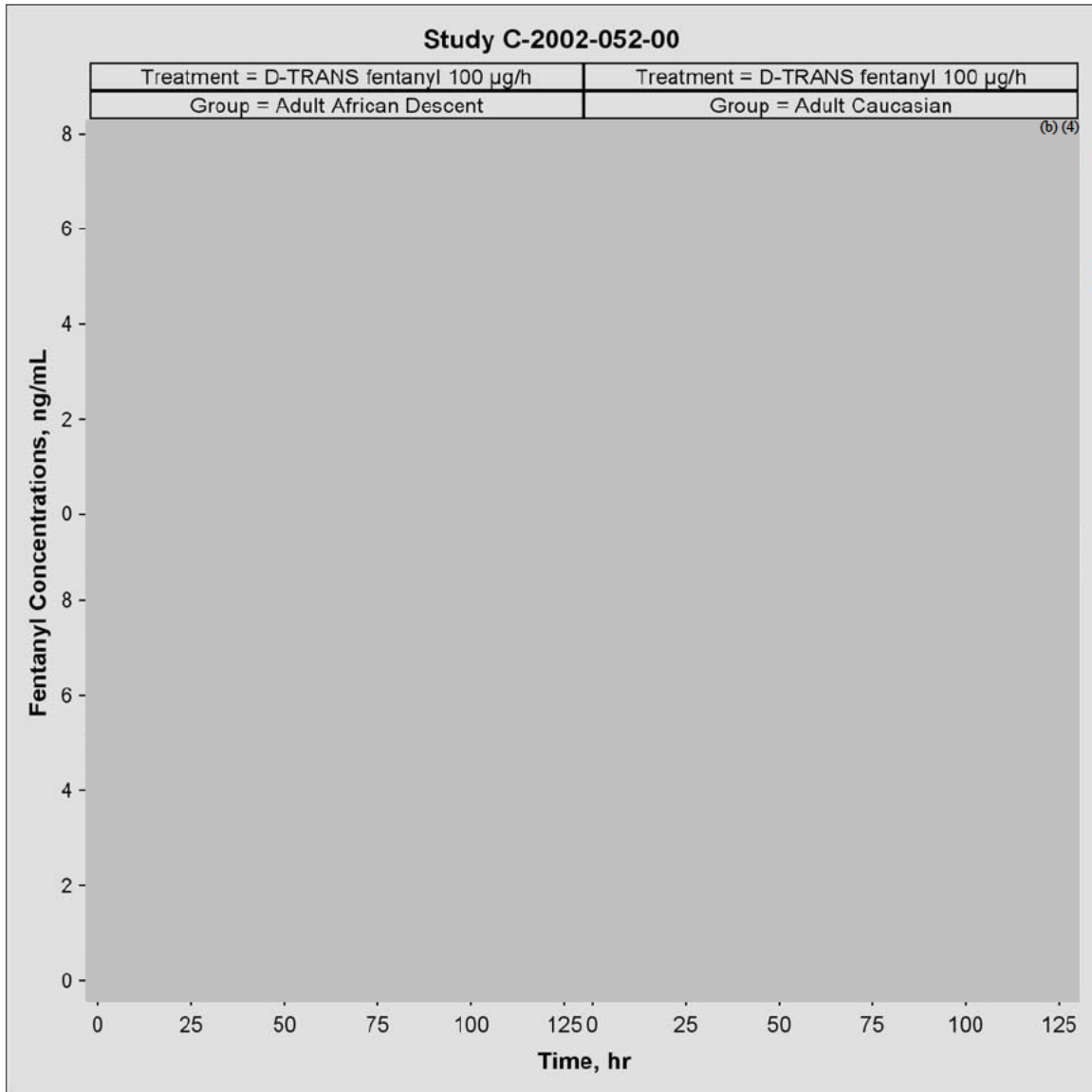
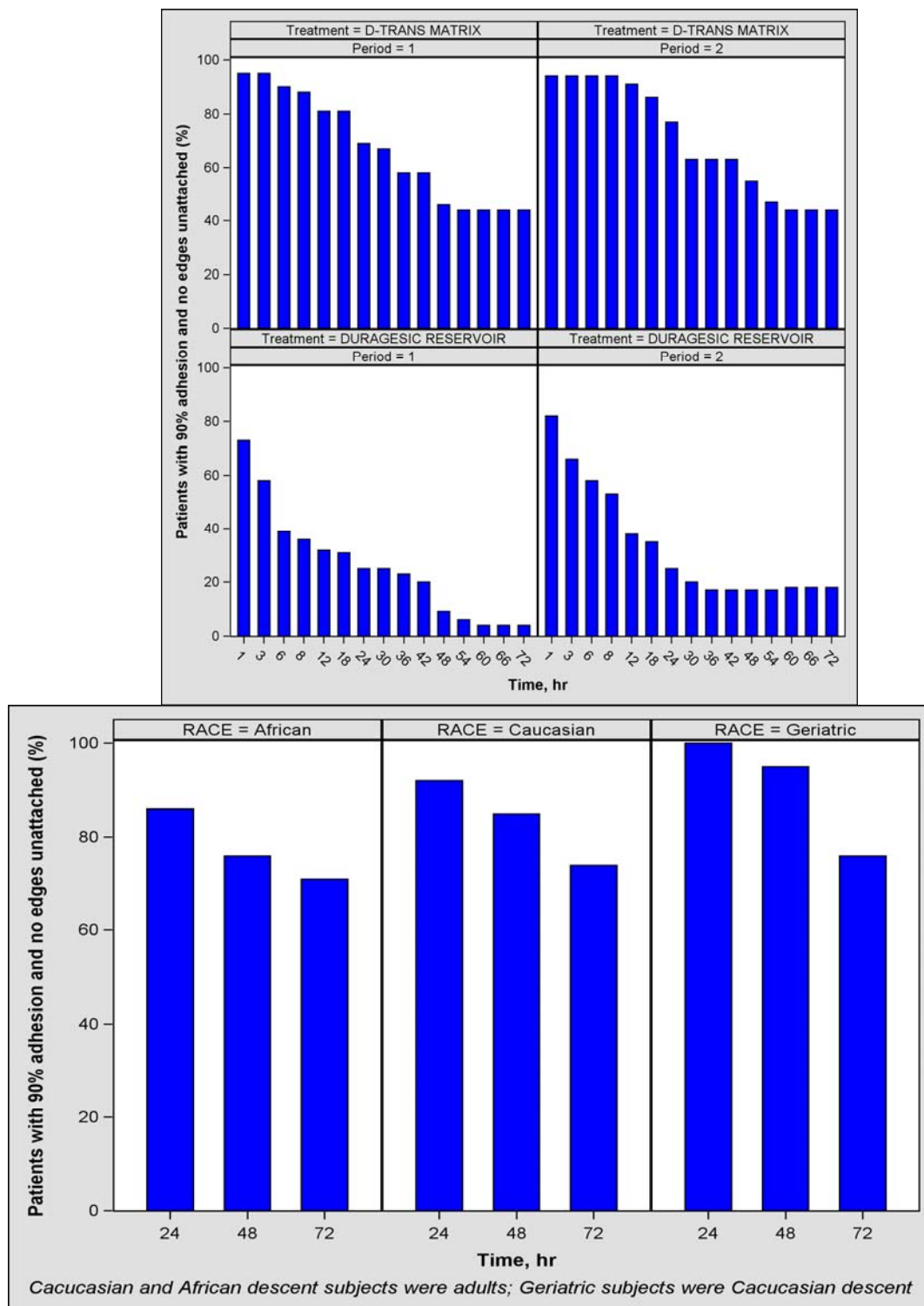


Figure 20: Study C-2002-052-00



4.2 Plots of adhesion for the pivotal BE study and race effect



Study FEN-PAI-1019: A Pivotal Bioequivalence Study Assessing Transdermal D-TRANS Fentanyl 100 µg/h Matrix System to DURAGESIC® Fentanyl 100 µg/h Reservoir System After Single Application in Healthy Subjects.

Principal Investigator: Michelle Ababa, M.D.

Publication (Reference): None.

Study Period: 26 September 2008 to 1 December 2008.

Phase of Development: Phase 1

Objectives: to evaluate the bioequivalence of D-TRANS fentanyl 100 µg/h matrix system to DURAGESIC fentanyl 100 µg/h reservoir system after single application in healthy subjects. Additionally, safety of the subjects was evaluated throughout the study.

Methods: This was a single-center, randomized, open-label, single application, 2-period crossover study in healthy adult subjects. All screening procedures were performed to determine eligibility within 21 days before admission to the research facility. After satisfactorily completing the naloxone challenge test on Day -1 of Period 1, subjects who met the selection criteria were randomly assigned to 1 of the 2 treatment sequences: Treatment Sequence 1 (AB) or Treatment Sequence 2 (BA).

- Treatment A: DURAGESIC 100 µg/h reservoir system applied for 72 hours
- Treatment B: D-TRANS 100 µg/h matrix system applied for 72 hours

Each system was worn on the lateral aspect of upper, outer arm. The treatment received during Period 2 was placed on the contra-lateral arm. Successive treatment periods were separated by a washout period of 8 to 14 days. Subjects remained at the study site from Day -1 until completion of the 120-hour postdose pharmacokinetic blood sample collection on Day 6 of each treatment period. During this study 2 opioid antagonists were used:

- Naltrexone hydrochloride tablets to continuously block the effect of fentanyl delivered through the DURAGESIC and D-TRANS systems; and
- Naloxone hydrochloride injectable that was used for the opioid challenge test performed on Day -1 of Period 1, and as a rescue medication if required.

Number of Subjects (planned and analyzed): Ninety-one healthy men or women were enrolled so that 74 subjects completed both treatment periods and provided pharmacokinetic data for both DURAGESIC and D-TRANS systems.

Diagnosis and Main Criteria for Inclusion: Healthy men or women between 18 to 55 years of age, inclusive with body mass index between 18 to 30 kg/m² at screening; no clinically relevant abnormalities as determined by: medical history, physical examination, vital signs, blood chemistry, complete blood count, urinalysis, and electrocardiogram; negative naloxone challenge test; negative urine drug test and alcohol test at screening and 24 hours before start of treatment initiation in each treatment period; subjects were to D-TRANS (Fentanyl Transdermal Patch): Clinical Study Report Synopsis FEN-PAI-1019

utilize a medically acceptable method of contraception throughout the entire study period including the washout period and for 3 months (men) or 1 week (women) after the study was completed.

Test Product, Dose and Mode of Administration, Batch No.: D-TRANS fentanyl 100 µg/h matrix system applied to the lateral aspect of the subject's upper arm for 72 hours. Lot No.: A06374-001L02, Package Lot Number: T94935, Expiration date: 08/2010.

Reference Therapy, Dose and Mode of Administration, Batch No.: DURAGESIC fentanyl 100 µg/h reservoir system applied to the lateral aspect of the subject's upper arm for 72 hours. Lot No.: A06374-001L01, Package Lot Number: T94934, Expiration date: 06/2010.

Commercially available naltrexone and naloxone were provided by the site. Naloxone: Lot No.: 65-343-EV, 52-111-EV (expiration date: 05/2010, and 04/2009, respectively). Naltrexone: Lot No.: 170L62812, 1170L60943, and 1170M66473 (expiration date: 09/2009, 03/2009, and 05/2010 respectively).

Duration of Treatment: was approximately 28 days (two 7-day treatment periods and one ≤14 day washout period between dose administration). The screening period was to be completed within 21 days before Check-in for Period 1.

Criteria for Evaluation:

Pharmacokinetic Evaluations: During each treatment period, serial blood samples were collected before and for 120 hours following the initiation of each treatment. Both the D-TRANS and DURAGESIC transdermal systems were applied to each subject for 72 hours, 1 system per treatment period. The following key serum pharmacokinetic parameters were calculated: C_{max} , t_{max} , AUC_{last} , AUC_{∞} , $t_{1/2}$, and λ_{z-} .

Skin Assessments: The skin site to which D-TRANS and DURAGESIC transdermal systems were applied was monitored for the development of topical adverse events (AEs) (erythema, edema, papules, pustules, and itching) at 1 and 24 hours after removal of each system.

System Functionality: Assessments of system adherence occurred each time vital signs were collected. Additionally adherence scores of the systems were recorded at 24, 48, and 72 hours post system application.

Safety Assessments: Safety was evaluated by examining the incidence and type of AEs, skin assessments at the application sites (after removal of the systems), and changes in clinical laboratory test values, physical examination results, vital signs, pulse oximetry measurements, and sleeping respirations from the screening phase through study completion, including the washout interval.

Statistical Methods:

Sample size: Using an estimate of 20% for intrasubject coefficient of variation (CV) for AUCs and C_{max} , a sample size of 74 subjects was sufficient to conclude the bioequivalence (confidence intervals of the geometric mean to fall within 80% to 125%) of the D-TRANS matrix system and the DURAGESIC reservoir system with a power of 80% when the true ratio of the means of the 2 products was equal to 115%. Ninety-one subjects enrolled in the study and 74 subjects completed all assigned treatments.

Pharmacokinetic Analysis: Mixed-effects models were fitted to the data with the logarithm of AUCs and C_{max} as the dependent variables, treatment-sequence group, period, and treatment (A and B) as fixed effects, and subject as a random effect. The estimated least square means and intrasubject variance from the mixed-effects model was used to construct 90% confidence intervals for the differences in means on a log scale between D-TRANS and DURAGESIC. The limits of the confidence intervals were retransformed using anti-logarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters of treatment B versus A.

Safety Analysis: All subjects who received study medication were included in the safety evaluation. Early termination data, AEs, vital signs, concomitant medications and laboratory data were listed.

RESULTS:

Of the 91 randomized subjects, 74 (81%) completed the study. Of the 17 withdrawn subjects, 1 due to AEs, 1 due to pregnancy, 11 withdrew consent, and 4 were withdrawn due to other reasons. Of the 91 randomized subjects, 50 were men and 41 were women. For both sequences, the mean age and the BMI were comparable and within specified study criteria.

PHARMACOKINETIC RESULTS: The systemic exposure of fentanyl (as measured by serum C_{max} and AUC values) and the time to reach maximum fentanyl concentrations (t_{max}) were comparable across treatments. The mean half-life values ranged between 26 and 27 hours for both treatments.

Mean ($\pm$ SD) Serum Fentanyl Pharmacokinetic Parameters After a Single Application of both the DURAGESIC (Reservoir) and D-TRANS (Matrix) Fentanyl 100 μ g/hr Systems (Pharmacokinetic Analysis Set)

Treatment	D-TRANS 100 μ g/hr (Test)			DURAGESIC 100 μ g/hr (Reference)		
	n	Mean $\pm$ SD	%CV	n	Mean $\pm$ SD	%CV
PK Parameters						
C_{max} (ng/mL)	79	2.39 $\pm$ 1.07	45.0	81	2.30 $\pm$ 0.83	35.9
t_{max} (h) ^a	79	42.0 (8.0 – 78.0)	--	81	42.0 (18.0 – 78.0)	--
AUC_{last} (ng•h/mL)	79	147 $\pm$ 53.9	36.7	81	136 $\pm$ 40.8	30.0
AUC_{∞} (ng•h/mL)	79	167 $\pm$ 63.6	38.2	81	155 $\pm$ 52.4	33.7
$t_{1/2}$ (h)	79	26.9 $\pm$ 8.9	33.3	81	26.0 $\pm$ 9.1	34.9

^a t_{max} reported as median (min – max)

The estimated ratio of mean pharmacokinetic parameters of fentanyl and 90% CIs of the pharmacokinetic parameters of fentanyl are presented in the table below. The ratio of the geometric means between the DURAGESIC and D-TRANS treatments for C_{max} , AUC_{last} , and AUC_{∞} , were 105.83%, 109.96%, and 109.71%, respectively. The 90% CIs of the ratios of the geometric means for all fentanyl PK parameters were contained within the bioequivalence criteria of 80% to 125%.

Estimated ratio of geometric means and 90% confidence intervals for the Ratio Between the
DURAGESIC (Reservoir) and D-TRANS (Matrix) Fentanyl 100 µg/hr Systems
(Statistical Analysis Set)

PK Parameter	Intra-subject CV (%)	Geometric Means		90% Confidence Intervals		
		D-TRANS 100 µg/hr (Test)	DURAGESIC 100 µg/hr (Reference)	Ratio (Test/Ref, %)	Lower limit (%)	Upper limit (%)
C _{max} (ng/mL)	18.7	2.26	2.13	105.83	100.58	111.36
AUC _{last} (ng•h/mL)	13.0	141.60	128.77	109.96	106.14	113.92
AUC _∞ (ng•h/mL)	14.3	159.92	145.76	109.71	105.51	114.08
N=74						

SYSTEM FUNCTIONALITY: All systems were adhered to ≥75% of the application-site area with no edges unattached for the 72-hour-wearing period. The D-TRANS system had a greater percentage of subjects with ≥90% adherence than the DURAGESIC system in both periods at all time points.

SAFETY RESULTS: No death or serious AEs were reported. The AEs reported in this study were: 18 (22%) during D-TRANS treatment and 17 (20%) during DURAGESIC treatment. AEs were all of mild to moderate severity. One subjects discontinued due to AEs (vomiting) considered mild, and possibly related to the study. The most common AEs in this study (>5% of subjects in either group) vomiting, headache and nausea, occurred with both treatments and are known effects of fentanyl and naltrexone. No changes in clinical laboratory test results or vital signs were considered clinically significant.

Five subjects had application site reactions (ASRs) recorded based on the Skin Site Assessments. Noticeable erythema (the mildest category, grade 1), ≤50% occluded area observed in 3 subjects (2 in DURAGESIC treatment group and 1 in D-TRANS treatment group) 1 hour after removal of the systems. D-TRANS (Fentanyl Transdermal Patch): Clinical Study Report Synopsis FEN-PAI-1019

One ASR of each of the following was recorded, all from the DURAGESIC treatment group: papules with ≤50% of the occluded area, and itching of mild severity. All but 1 (papules with ≤50% of the occluded area) of the application site reactions were resolved within 24 hours after system removal.

STUDY LIMITATIONS: [No notable study limitations were identified by the Sponsor.

CONCLUSION: The 100 µg/hr D-TRANS fentanyl matrix system was bioequivalent to the 100 µg/hr DURAGESIC fentanyl reservoir system. The D-TRANS fentanyl matrix system and the DURAGESIC fentanyl reservoir system were considered safe and well tolerated when concomitantly administered with naltrexone in this healthy subject population.

4.3 Study C-2002-047-04: A Study Comparing the Pharmacokinetics of Transdermal D-TRANS® Fentanyl 100 µg/h Matrix System After Single and Repeated Applications

Investigator/Study Center: Stuart J Mair, MBChB, DRCOG, DCPSA/Inveresk Clinical Research Ltd, Edinburgh, Scotland		
Publication (reference): none		
Study period: First subject treated: 11 February 2003 Last subject completed: 19 March 2003		Phase of Development: 1
Objective: To compare the pharmacokinetics of transdermal D-TRANS® fentanyl matrix system 100 µg/h (D-TRANS® fentanyl 100 µg/h) after single and repeated applications.		
Methodology: This was a single-center, open-label, 2-treatment, 2-period, sequential design study. Each subject received 2 treatments of D-TRANS® fentanyl 100 µg/h with a 6- to-14-day washout period between treatments. The washout period commenced upon removal of the transdermal study system. Before the first treatment period, each subject was challenged with naloxone to ensure that he/she was not dependent on opioids. Each subject received naltrexone 50 mg as the opioid antagonist twice daily, starting 14 hours before system application, during application, and through 24 hours post system removal. Subjects were randomly assigned to wear the study systems on the upper outer arm, upper chest, or upper back.		
Number of subjects (planned and analyzed): Planned, n=36. Enrolled and received at least 1 D-TRANS® fentanyl 100 µg/h system, n=36. Completed 2 treatments, n=33.		
Diagnosis and main criteria for inclusion: Healthy male and female subjects between 18 and 45 years of age who provided written consent to participate and did not have a history of or show the presence of drug or alcohol dependence or abuse.		
Test product, dose and mode of administration, batch number:		
	Treatment A	Treatment B
Nominal Dose	D-TRANS® fentanyl matrix system 100 µg/h 1 system worn for 72 h (single application)	D-TRANS® fentanyl matrix systems 100 µg/h 4 systems applied consecutively, each system worn for 72 h for a total wearing period of 288 hours (repeated applications)
Mode of administration	Transdermal delivery	
Code number	0013167	
Control number	0300817	
Fentanyl content	16.8 mg	
Duration of treatment	72 hours	288 hours

Duration of individual participation: approximately 4 weeks						
Duration of trial: 5 weeks						
Reference therapy: none						
Additional drugs per protocol: Naltrexone hydrochloride tablet, 50 mg twice daily Naloxone hydrochloride 0.8 mg subcutaneously, once (challenge test)						
Criteria for evaluation:						
<i>Pharmacokinetics:</i> Blood samples were collected at the time points specified below:						
	Single-application Treatment (single 72-h application)	Washout Period (6-14 days)	Repeated-applications Treatment (4 consecutive 72-h applications)			
	System 1		System 1	System 2	System 3	System 4
Post treatment initiation (hours)	0 ^a , 0.5, 1, 2, 3, 5, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72 ^b , 73, 74, 78, 84, 96, 108, 120		0 ^a , 72 ^c	144 ^c (C ₁₄₄)	216 ^c (C ₂₁₆)	216.5, 217, 218, 219, 221, 224, 228, 234, 240, 246, 252, 258, 264, 270, 276, 282, 288 ^b (C ₂₈₈), 289, 290, 294, 300, 312, 324, 336
^a Hour 0 = treatment initiation. Blood sample drawn before system applied. ^b System removal: Blood sample drawn before system removed. ^c System removal: Blood sample drawn before system removed. This was the predose sample before the next system was applied.						
System Functionality: The adherence of each D-TRANS [®] system was assessed at 24 and 48 hours after application and just before system removal (ie, 72 hours). Safety: Adverse events (AEs) and vital signs (blood pressure, temperature, pulse and respiratory rate) were monitored. AEs at the system application site (erythema, edema, papules, pustules, and itching) assessed at prescheduled time points (1 hour, and 24 hours post-system removal) were defined as topical AEs. AEs at the system application site at time points outside the scheduled observations or of a different nature than the topical AEs were reported as application site reactions (ASRs).						
Statistical methods: <i>Pharmacokinetic Measures:</i> Descriptive statistics were calculated for the pharmacokinetic parameters for both the single- (C _{max} , T _{max} , k, t _{1/2} , AUC ₍₀₋₇₂₎ , AUC _t , AUC ₍₀₋₁₂₀₎ , and AUC _{inf}) and repeated-application (C ₁₄₄ , C ₂₁₆ , C ₂₈₈ , C _{max} , T _{max} , k, t _{1/2} , and AUC _{ss}) treatments. Serum fentanyl concentrations C ₁₄₄ , C ₂₁₆ , and C ₂₈₈ were compared to evaluate whether the steady-state conditions had been reached after wearing 4 consecutive study systems in treatment Period 2. An ANOVA model was used for the analysis of log-transformed fentanyl pharmacokinetic parameter (AUC) (Chow & Liu, 1992). The least square estimate and the 90% confidence interval (CI) for ratios of mean parameters AUC _{ss} /AUC _{inf} (log transformed) for the 2 treatments (repeated/single applications) are presented (Schiirmann 1987). The ANOVA model included treatment, area-of-application, and treatment-by-area of application as fixed effects, and subject-within-area-of-						

Statistical methods continued:

application as a random effect. The Student-Newman-Keuls test was used to further compare application areas. The comparison among the application areas was not expected to have sufficient power since it was not the objective of the study. The accumulation ratio was calculated by AUC ($AUC_{(216-288)} / AUC_{(0-72)}$) and C_{max} ($C_{max,ss} / C_{max,1}$).

System Functionality and Safety Measures: Data were summarized, and descriptive statistics were calculated.

Pharmacokinetic Results:

Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values for Subjects Who Completed Both Treatments

Parameter	D-TRANS [®] fentanyl 100 µg/h single application n=33	D-TRANS [®] fentanyl 100 µg/h repeated applications n=33
C_{max} (ng/mL)	3.15 (1.08)	4.20 (1.16)
T_{max} (h)	23.6 (10.4)	19.7 (9.1)
$t_{1/2}$ (h) (terminal half-life) ^a	19.9 (5.8)	23.5 (7.2) ^b
k (h ⁻¹) (elimination rate constant)	0.038 (0.011)	0.032 (0.010) ^b
$AUC_{(0-72)}$	144 (43)	NA
AUC_t (ng·h/mL)	176.8 (52.6)	NA
$AUC_{(0-120)}$	176.8 (52.5)	NA
AUC_{inf} (ng·h/mL)	185.4 (55.8)	NA
$AUC_{(216-288)}$ (ng·h/mL)	NA	203.9 (52.8)

^a The terminal half-life was determined after the system was removed.

^b n=32

NA=Not applicable

The serum fentanyl concentration values at the end of the 2nd (C_{144}), 3rd (C_{216}), and 4th (C_{288}) consecutive 72-hour system applications were not significantly different (overall p value = 0.179) for the repeated applications, suggesting that steady state was reached by the 3rd consecutive system application. The mean (111%) and the 90% CI (106%-116%) for the ratios of log-transformed mean parameters AUC_{inf} and $AUC_{(216-288)}$ comparing single versus repeated applications of the D-TRANS[®] fentanyl 100 µg/h system were within the criteria (80% to 125% range) used for determining bioequivalence. This suggests the pharmacokinetics of fentanyl does not change with repeated application. The mean accumulation ratios comparing the single versus repeated applications were approximately 144% (by AUC) and approximately 139% (by C_{max}).

Pharmacokinetic Results continued:

The log-transformed AUC values were significantly different among the 3 different application areas (upper outer arm, upper chest, and upper back). However, the comparison was not carried out with sufficient power since it was not the objective of the study and should be interpreted with care.

Safety results: No serious AEs were reported, and all AEs were of mild or moderate severity. Adverse events were reported by 47.2% of subjects during the single-application treatment and by 58.8% during the repeated-applications treatment. The most frequently reported AEs (>10% of subjects with either treatment), abdominal pain and headache, have been reported during the use of commercially available transdermal fentanyl and/or oral naltrexone. All of these events were of mild or moderate severity and assessed by the study investigator as treatment related. Two subjects discontinued during the first treatment period because of AEs considered possibly related to study drug: moderate nausea and moderate vomiting in one subject and moderate purpuric rash in another. Most topical AEs were mild and resolved within 24 hours. Erythema was the most common topical AE; the majority of these events were identified as noticeable redness, the mildest category. No changes in clinical laboratory test results or vital signs were considered clinically significant.

Conclusions: Steady state was achieved by the 3rd consecutive 72-hour system application. A comparison of the AUC values following the first application (AUC_{inf}) and at steady state (AUC_{ss}) suggests that the pharmacokinetics of fentanyl does not change with repeated application.

No serious AEs were reported, and all AEs were of mild or moderate severity. No new safety issues were identified with D-TRANS[®] fentanyl in this subject population, and the system was well tolerated.

Date of the report: 25 June 2003

4.4 Study C-2002-048-00: A Pharmacokinetic Study Evaluating the Dose Relationship of Transdermal D-TRANS® Fentanyl Matrix Systems

Investigator(s)/Study Center: Dr. Riadh Jazrawi, MBChB, MSc, PhD/ Charterhouse Clinical Research Unit, Ravenscourt Park Hospital, London, UK				
Publication (reference): none				
Study period: First subject treated: 8 April 2003 Last subject completed: 25 May 2003		Phase of Development: 1		
Objective: To evaluate the dose relationship of D-TRANS [®] fentanyl matrix systems 25, 50, 75, and 100 µg/h (D-TRANS [®] fentanyl 25, 50, 75, and 100 µg/h).				
Methodology: This was a single-center, randomized, single-dose, open-label, 4-treatment, 4-sequence, 4-period, crossover study. Each subject received 4 treatments of D-TRANS [®] fentanyl (25, 50, 75, and 100 µg/h) with a 6-to-14-day washout period between treatments. The D-TRANS [®] fentanyl system was worn for 72 hours during each treatment period. Subjects were randomly assigned to wear the study systems on the upper outer arm, upper chest, or upper back. In each period, 25 blood samples were taken at specified times for fentanyl pharmacokinetic analysis. Before the first treatment period, each subject was challenged with naloxone to ensure that he/she was not dependent on opioids. Additionally, each subject received naltrexone 50 mg as the opioid antagonist starting 14 hours before system application, then twice daily during application through 24 hours post-system removal.				
Number of subjects (planned and analyzed): Planned, n=36. Enrolled and received at least 1 D-TRANS [®] fentanyl system, n=36. Completed all 4 treatments, n=31.				
Diagnosis and main criteria for inclusion: Healthy male and female subjects between 18 and 45 years of age who provided written consent and who did not have a history of or show the presence of drug or alcohol dependence or abuse and who met inclusion/exclusion criteria were included in the study.				
Test product, dose and mode of administration, batch number:				
Dose	Treatment A D-TRANS [®] fentanyl 25 µg/h	Treatment B D-TRANS [®] fentanyl 50 µg/h	Treatment C D-TRANS [®] fentanyl 75 µg/h	Treatment D D-TRANS [®] fentanyl 100 µg/h
Mode of administration	Transdermal delivery			
Code number	0012976	0012977	0012978	0012979
Control number	0223247	0223250	0223253	0223257
Fentanyl content	4.2 mg	8.4 mg	12.6 mg	16.8 mg

Duration of individual participation	5-7 weeks
Duration of treatment	72 hours
Duration of trial	7 weeks
Reference therapy: none	
Additional drugs per protocol: Naltrexone hydrochloride tablet, 50 mg, oral, twice daily Naloxone hydrochloride 0.8 mg, subcutaneous, once (challenge test)	
Criteria for evaluation: <i>Pharmacokinetics:</i> Blood samples were collected from each subject during each treatment at pre-dose and at 0.5, 1, 2, 3, 5, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 73, 74, 78, 84, 96, 108, and 120 hours after system application. The adherence of each D-TRANS[®] system was assessed at 24 and 48 hours after application and just before system removal (ie, 72 hours or earlier if the system was removed before 72 hours). <i>Safety:</i> Adverse events (AEs) and vital signs (blood pressure, temperature, pulse and respiratory rate) were monitored. AEs at the system application site (erythema, edema, papules, pustules, and itching) assessed at prescheduled time points (1 hour and 24 hours post-system removal) were defined as topical AEs. AEs at the system application site at time points outside the scheduled observations or of a different nature than topical AEs were reported as application site reactions (ASRs).	
Statistical methods: Descriptive statistics were calculated for the serum fentanyl pharmacokinetic parameters of C_{max}, T_{max}, k, $t_{1/2}$, AUC_t, $AUC_{(0-120)}$, and AUC_{inf} for each treatment. Regression analyses were performed on AUC_{inf} and C_{max} as a function of dose. Assuming the standard deviations of pharmacokinetic parameters for different dose levels were proportional to the dose level, a mixed-effect analysis of variance (ANOVA) model was also used in the analysis of dose linearity. This model was to include sequence, application area, treatment, period, and treatment-by-area of application as fixed effects, and subject-within-sequence as a random effect. The SAS PROC MIXED procedure was used for this analysis. The Student-Newman-Keuls test was to be used to further compare application areas.	

Changes in Planned Analysis: The Wilcoxon rank-sum test was used to compare fentanyl $T_{\max}$ values for the 4 treatments, using a 0.05 significance level.

In the mixed-effect ANOVA model used to evaluate dose linearity, the effect of application area was modified to application area nested within treatment sequence, and the random effect of subject-within-sequence was modified to subject-within-(sequence and application area).

An additional ANOVA model was used for the analysis of log-transformed fentanyl pharmacokinetic parameters (AUC_t , AUC_{inf} , $C_{\max}$ [dose normalized to 25 $\mu\text{g/h}$], and $t_{1/2}$). This ANOVA model included sequence, application area within treatment sequence, treatment, period, and treatment-by-area of application as fixed effects, and subject-within-(sequence and application area) as a random effect.

The effect of application area was not significant in the analysis of dose-normalized, log-transformed pharmacokinetic parameters ($C_{\max}$ and AUC_{inf}) using the ANOVA model; therefore, the Student-Newman-Keuls test was not performed to further compare the difference among application areas.

Pharmacokinetic Results:

Mean (SD) values for serum fentanyl pharmacokinetic parameters for the 31 subjects who completed the 4 treatments are summarized below. Mean $C_{\max}$ and AUC values increased proportionally with increasing D-TRANS[®] fentanyl dose. $T_{\max}$ values were not significantly different between treatments ($p=0.37$). Mean $t_{1/2}$ values were similar across all 4 treatments.

Serum Fentanyl Pharmacokinetic Parameters				
Mean (SD)				
n=31				
Parameter	D-TRANS [®] fentanyl 25 µg/h	D-TRANS [®] fentanyl 50 µg/h	D-TRANS [®] fentanyl 75 µg/h	D-TRANS [®] fentanyl 100 µg/h
C _{max} (ng/mL)	0.85 (0.26)	1.72 (0.53)	2.32 (0.86)	3.36 (1.28)
T _{max} (h)	31.69 (16.50)	32.78 (15.61)	35.82 (14.08)	29.88 (13.26)
t _{1/2} (h) ^a	21.6 (7.0)	23.0 (8.1)	23.7 (9.1)	21.6 (7.4)
AUC _t (ng.h/mL) ^b	51.4 (14.9)	100.4 (26.7)	146.6 (46.2)	196.4 (59.3)
AUC _{inf} (ng.h/mL)	55.0 (16.3)	108.7 (30.9)	159.4 (50.1)	210.7 (63.7)
^a n=30 for D-TRANS [®] fentanyl 100 µg/h ^b AUC ₍₀₋₁₂₀₎ was the same as AUC _t Source: Tables 11.1.2.1, 11.1.2.2, 11.1.2.3 Results of linear regression analyses and the mixed-effect ANOVA model used to evaluate dose linearity indicate that fentanyl AUC _{inf} and C _{max} values increase linearly with the fentanyl doses tested in this study (D-TRANS [®] fentanyl 25, 50, 75, and 100 µg/h). Results of the analysis of dose-normalized, log-transformed serum fentanyl pharmacokinetic parameters for the 31 subjects who completed the 4 treatments are presented in the following table. The 90% confidence interval (CI) for dose-normalized, log-transformed AUC _t , AUC _{inf} , and C _{max} for all treatment comparisons fell within the bioequivalence criteria of 80% to 125%. Results of this analysis indicate that the pharmacokinetics of fentanyl is linear and dose proportional.				

Statistical Analysis of Log-transformed Parameters for Serum Fentanyl Following Fentanyl Treatments, Dose Normalized to 25 µg/h (n=31)				
Parameter	Ratio (%)	Power ^a (%)	90% CI	
			Lower (%)	Upper (%)
Bioequivalence of 50 µg/h and 25 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	97.59	>99	91.67	103.89
lnAUC _{inf}	98.32	>99	92.46	104.54
lnC _{max}	100.36	>99	93.30	107.95
Bioequivalence of 75 µg/h and 25 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	94.49	>99	88.77	100.58
lnAUC _{inf}	96.02	>99	90.32	102.09
lnC _{max}	89.76	>99	83.46	96.53
Bioequivalence of 100 µg/h and 25 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	95.50	>99	89.71	101.67
lnAUC _{inf}	95.68	>99	89.98	101.74
lnC _{max}	97.33	>99	90.48	104.69
Bioequivalence of 75 µg/h and 50 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	96.82	>99	90.95	103.08
lnAUC _{inf}	97.67	>99	91.85	103.85
lnC _{max}	89.44	>99	83.15	96.20
Bioequivalence of 100 µg/h and 50 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	97.87	>99	91.94	104.17
lnAUC _{inf}	97.32	>99	91.53	103.46
lnC _{max}	96.98	>99	90.18	104.30
Bioequivalence of 100 µg/h and 75 µg/h D-TRANS [®] Fentanyl Dose Normalized to 25 µg/h				
lnAUC _t	101.08	>99	94.94	107.61
lnAUC _{inf}	99.64	>99	93.70	105.95
lnC _{max}	108.43	>99	100.81	116.63
^a Power to detect a difference equal to 20% of the reference mean, at a significance level of 0.05, expressed as a percentage of the reference mean. Source: Table 11.1.2.4, Appendix 12.1.9.1				

System Functionality Results: Most systems adhered to at least 90% of the application-site area with no edges unattached at 24 hours, 48 hours, and 72 hours, with 1 exception. At the 72-hour assessment, an equal number of D-TRANS[®] fentanyl 100 µg/h systems were adhered to at least 90% of the application-site area as were adhered to less than 90%. None of 100 µg/h systems required taping at any assessment time point.

Safety Results:

No serious AEs were reported. Most AEs were of mild or moderate severity. Adverse events (excluding ASRs) were reported by 36.4%, 46.9%, 45.5%, and 38.7% of subjects during D TRANS[®] fentanyl 25, 50, 75, and 100 µg/h, respectively. The most frequently reported AEs (≥10% of subjects during any treatment) classified as probably or possibly related to treatment were headache and nausea. Both of these events are known to be associated with transdermal fentanyl and/or oral naltrexone treatment. Two subjects discontinued the study because of an AE: mild nausea, considered possibly related to study drug, in 1 subject and moderate upper respiratory tract infection, judged not related to study drug, in another.

Most of the subjects on study had no ASRs; 5 subjects reported a total of 6 ASRs. All ASRs were judged treatment related, and all but 1 were of mild severity.

At the 24-hour post-system removal assessment, most subjects (74% to 100%) had no topical AEs. Most topical AEs were of mild severity. Erythema was the most common topical AE; the majority of events were identified as noticeable redness, the mildest category. In general, topical AEs were similar among the 4 treatments.

No changes in clinical laboratory test results or vital signs were considered clinically significant.

Conclusions:

The results of the linear regression and dose-normalized fentanyl pharmacokinetic parameter analyses indicate that the pharmacokinetics of fentanyl is linear and dose proportional between the D-TRANS[®] fentanyl 25, 50, 75, and 100 µg/h systems.

The majority of systems were adhered to at least 90% of the application area with no edges unattached at most assessment time points.

No serious AEs were reported, and no new safety issues were identified in this study. All dosage strengths of D-TRANS[®] fentanyl were well tolerated, and the systemic and topical safety was similar for all 4 treatments.

Date of the report: 24 July 2003

Study C-2002-052-02: Evaluation of Fentanyl Pharmacokinetics in Two Skin Types and Age Groups Following a Single Application of D-TRANS® Fentanyl 100 µg/h Matrix System

Investigator(s)/Study Center: Riadh Jazrawi, MBChB, MSc, PhD/Charterhouse Clinical Research Unit, Ravenscourt Park Hospital, Ravenscourt, London	
Publication (reference): none	
Study period: First subject treated: 2 April 2003 Last subject completed: 18 May 2003	Phase of Development: 1
Objective: To evaluate the effect of skin type and age on the pharmacokinetics of D-TRANS® fentanyl 100 µg/h matrix system (D-TRANS® fentanyl 100 µg/h) following a single application.	
Methodology: This was a single center, open-label study in 3 groups of healthy subjects: fair-skinned Caucasians 18 to 45 years old, dark-skinned subjects of African descent 18 to 45 years old, and fair-skinned Caucasians ≥65 years old. Each subject had D-TRANS® fentanyl 100 µg/h applied to a skin site on the upper outer arm and wore the system for 72 hours. Prior to system application, each subject was challenged with naloxone to ensure that he/she was not dependent on opioids. Each subject received a naltrexone 50 mg tablet as the opioid antagonist starting 14 hours before system application, twice daily during application, and ending 24 hours post system removal.	
Number of subjects (planned and analyzed): Planned n=72; Enrolled n=71; Completed n=69 (fair-skinned Caucasians 18 to 45 years old [n=27], dark-skinned subjects of African descent 18 to 45 years old [n=21], and fair-skinned Caucasians ≥65 years old [n=21]).	
Diagnosis and main criteria for inclusion: Healthy male or female subjects between 18 and 45 years of age who were Caucasian (Luminance [L*] values ≥60), or of African descent (L* values ≤48) or Caucasian (L* values ≥60) who were ≥65 years of age. All subjects had to provide written consent, have no history of or show the presence of drug or alcohol dependence or abuse and meet inclusion/exclusion criteria.	
Test product, dose and mode of administration, batch number:	
Treatment/Dose	D-TRANS® fentanyl 100 µg/h worn for 72 h
Mode of administration	Transdermal delivery
Code number	0013167
Control number	0300817
Fentanyl content	16.8 mg
Duration of treatment	72 hours per treatment period
Duration of individual participation	10-40 days
Duration of trial	6 weeks
Reference therapy: None	
Additional drugs per protocol: Naltrexone hydrochloride tablet, 50 mg twice daily Naloxone hydrochloride subcutaneously, 0.8 mg, once (challenge test)	

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected during treatment at: pre-dose and 0.5, 1, 2, 3, 5, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 73, 74, 78, 84, 96, 108, and 120 hours following system application.

System Functionality: Adherence of each system was assessed at 24 and 48 hours after application and just before system removal (ie, 72 hours or earlier if the system was removed before 72 hours).

Safety: Adverse events (AEs) and vital signs (blood pressure, temperature, pulse and respiratory rate) were monitored. AEs at the system application site (erythema, edema, papules, pustules, and itching) assessed at prescheduled time points (1 hour, and 24 hours post-system removal) were defined as topical AEs. AEs at the system application site at time points outside the scheduled observations or of a different nature than topical AEs, were reported as application site reactions (ASRs).

Statistical methods:

Pharmacokinetics: Descriptive statistics were calculated for pharmacokinetic parameters ($C_{\max}$, $T_{\max}$, k , $t_{1/2}$, AUC_t , and $AUC_{\inf}$) for each group.

System Functionality and Safety Measures: Data were summarized and descriptive statistics were calculated.

Pharmacokinetic Results:

The mean serum fentanyl concentration profile and the mean fentanyl pharmacokinetic parameters after a single application of D-TRANS[®] fentanyl 100 µg/h were similar for the adult Caucasian and adult African descent groups, both 18 to 45 years old.

Drug exposure ($AUC_{\inf}$) was also similar between the Caucasian subjects ≥65 years old and the subjects 18 to 45 years old. The observed serum fentanyl concentrations during the system wearing period and hence the mean $C_{\max}$ and AUC_t tended to be slightly lower in subjects ≥65 years old than subjects 18-45 years old. The mean $t_{1/2}$ value was longer in subjects ≥65 years old than subjects 18-45 years old. The longer $t_{1/2}$ observed in the older age group is consistent with literature (Durogesic[™] UK SPC; Bentley et al, 1982; Wood and Wood, 1990).

Intersubject variability in $AUC_{\inf}$ was lower (24 %, 95% CI [161.3, 194.3]) in Caucasian subjects 18-45 years old as compared to ≥65 years old and African descent group (58%, 95% CI [140.1, 240.1]) and 37%, 95% CI [158.2, 222.7]) respectively) and is reflected in the wider confidence interval.

Mean Values (SD) for Serum Fentanyl Pharmacokinetic Parameters for Subjects Who Completed the Study

Parameter	Adult Caucasian (n=27)	Adult African Descent (n=21)	Geriatric Caucasian (n=21)
C _{max} (ng/mL)	2.69 (0.66)	2.86 (1.07)	2.48 (1.60)
T _{max} (h)	35.1 (17.1)	39.2 (16.7)	49.7 (21.4)
t _{1/2} (h)	23.9 (9.8)	23.5 (8.0)	34.4 (14.1) ^a
AUC _t (ng.h/mL) ^b	164.1 (36.7)	173.8 (66.0)	153.3 (89.7)
AUC _{inf} (ng.h/mL)	177.8 (41.8)	190.4 (70.8)	190.1 (110)

^a n=19, half-life could not be determined for Subjects 307 and 313.

^b AUC_t was the same as AUC₍₀₋₁₂₀₎

System Functionality Results:

D-TRANS[®] fentanyl systems adhered well to all skin types in this study.

Safety Results:

No serious adverse events were reported in this study and no enrolled subject discontinued from the study because of an AE. All of the AEs reported were of mild (59 of 68) or moderate severity.

A similar proportion of subjects in each demographic group reported at least one AE, 13 of 27 subjects (48.1%) in the adult Caucasian group, 11 of 23 subjects (47.8%) in the adult African descent group, and 11 of 21 subjects (52.4%) in the geriatric Caucasian group.

The most frequently reported AEs (≥10% of subjects) by group were: nausea (5, 18.5%), headache (4, 14.8%), and dizziness (3, 11.1%) in the adult Caucasian group; headache (4, 17.4%) and nausea (3, 13.0%) in the adult African descent group; and constipation and nausea, each reported by 3 subjects (14.3%) in the geriatric Caucasian group. Most of the AEs reported by 2 or more subjects (eg, constipation, diarrhea, dizziness, headache, nausea, and somnolence) tended to be those associated with fentanyl or oral naltrexone and were generally assessed as probably or possibly related to treatment by the investigator.

No ASRs were reported.

Over 90% of the subjects in the adult Caucasian group and over 80% of the subjects in the adult African descent group had no topical AEs noted at 24-hours post-system removal. In the geriatric Caucasian group, only one subject had a topical AE, mild papules at the 24-hour assessment. Topical AEs observed in the other 2 groups at the 24-hour assessment were seen in 0-2 subjects in the Caucasian group and in 2-4 subjects in the African descent group.

Overall, there were no clinically significant changes in the vital signs, and laboratory and ECG tests for the study population.

Conclusions:

Fentanyl pharmacokinetic parameters were similar between adult (18-45 years) Caucasian and African descent groups. The overall drug exposure (AUC_{inf}) after a single application of D-TRANS[®] fentanyl 100 µg/h was also similar in all three populations. The mean $t_{1/2}$ value was longer in Caucasian subjects ≥65 years old than subjects 18-45 years old. Intersubject variability in AUC_{inf} was lower in Caucasian subjects 18-45 years old as compared to subjects ≥65 years old and subjects in the African descent group.

D-TRANS[®] fentanyl 100 µg/h adhered well to all skin types in this study.

D-TRANS[®] fentanyl 100 µg/h was well tolerated in healthy subjects 18 to 45 years old of Caucasian or African descent and in Caucasian subjects ≥65 years old. The systemic and topical safety of D-TRANS[®] fentanyl was similar in the three groups. No serious AEs were reported, all AEs were of mild or moderate severity, and no new safety issues were identified with D-TRANS[®] fentanyl in the study population.

4.5 Study C-2004-005-01: Effects of External Heat After Application of Duragesic® and D-TRANS® Fentanyl System to Healthy Volunteers

Investigator/Study Center: Gilbert R Weiner, DO, SFBC International, Inc. Miami, FL		
Publication (reference): None		
Study period: First subject treated: 28 March 2004 Last subject completed: 29 April 2004		Phase of Development: 1
Objectives: To evaluate the effects of external heat on serum fentanyl concentrations following the application of a Duragesic® 25 µg/h and a D-TRANS® fentanyl 25 µg/h system.		
Methodology: This was a randomized, single-center, open-label, 5-treatment, 5-period, 5-sequence, crossover study. Subjects received 25 µg/h Duragesic® and 25 µg/h D-TRANS® fentanyl, applied to the upper outer arm and worn for 36 hours. For 2 of the 5 treatments, external heat was applied at two 10-hour intervals: 0 to 10 hours, and then 26 to 36 hours post-system application. There was a 5- to 14-day washout period between treatments, which started after each system was removed. Each subject received naltrexone 50 mg as the opioid antagonist starting 14 hours before system application, then twice daily during application through 36 hours post-system removal. Treatment A: Duragesic® 25 µg/h fentanyl (36 hour application). No external heat applied Treatment B: Duragesic® 25 µg/h fentanyl (36 hour application). External heat applied at two 10-hr intervals: 0 to 10 hours, and then 26 to 36 hours post-system application Treatment C: D-TRANS® 25 µg/h fentanyl (36 hour application). No external heat applied Treatment D: D-TRANS® 25 µg/h fentanyl (36 hour application). External heat applied at two 10-hr intervals: 0 to 10 hours, and then 26 to 36 hours post-system application Treatment E: Duragesic® 50 µg/h fentanyl (36 hour application). No external heat applied		
Number of subjects (planned and analyzed): Planned n=25; Enrolled n=25 (25 received at least 1 treatment); Completed n=20		
Diagnosis and main criteria for inclusion: Healthy males and females between 18 and 45 years of age, inclusive, who provided written consent and who met enrollment criteria were included in the study.		
Test product, dose and mode of administration, batch number:		
Dose	D-TRANS® 25 µg/h fentanyl matrix system	
Mode of administration	Transdermal delivery	
Batch number	0223246	
Reference therapy, dose and mode of administration, batch number:		
Dose	Duragesic® 25 µg/h fentanyl	Duragesic® 50 µg/h fentanyl
Mode of administration	Transdermal delivery	
Batch number	0300921	0208353
Duration of individual participation: 6-8 weeks		
Additional drugs per protocol: During this study two opioid antagonists were used: Naltrexone hydrochloride tablets (50 mg 14 h prior to application, then twice daily until 36 hours after system removal) to continuously block the effect of fentanyl delivered through the transdermal study systems, and Naloxone hydrochloride injectable, which was used for the opioid challenge test (0.8 mg SC) and could have been used as rescue medication, if required.		
Criteria for evaluation:		

Pharmacokinetics: Blood samples for determination of serum fentanyl concentrations were collected from each subject during each treatment at the following time points: predose, 2, 4, 6, 8, 10, 12, 24, 26, 28, 30, 32, 34, 36 (prior to the system removal), 40, 48, 56, and 72 hours post system application. The adherence of each transdermal system was assessed at 24 hours and 36 hours, just prior to removal of the system.

Safety: Adverse events (AEs) and vital signs (blood pressure, temperature, pulse, and respiratory rate) were monitored. Adverse events at the system application site (erythema, edema, papules, pustules, and itching) assessed at prescheduled time points (1 hour and 24 hours post-system removal) were defined as topical AEs. Adverse events at the system application site at time points outside the scheduled observations or of a different nature than the topical AEs were reported as application site reactions (ASRs). Concomitant medications were recorded. Pregnancy, alcohol, and drug tests were performed at Day 0 of each treatment period. Standard laboratory tests, electrocardiogram (ECG), and physical examinations were done at screening and at study termination.

Statistical methods:

Pharmacokinetics: Descriptive statistics were calculated for the serum fentanyl PK parameters of $C_{max, 0-10}$, $C_{max, 26-36}$, $C_{max, 0-72}$, $T_{max, 0-10}$, $T_{max, 26-36}$, $T_{max, 0-72}$, k , $t_{1/2}$, AUC_t , AUC_{0-10} , AUC_{0-26} , AUC_{0-36} , and AUC_{inf} for each treatment. Mixed-effect analysis of variance (ANOVA) models were used in the analysis of log-transformed fentanyl PK parameters (AUC_{inf} and C_{max}). The ANOVA models included treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. The ratios of mean fentanyl PK parameters (log transformed AUC_{inf} and C_{max}) between pairwise Treatments B/A, D/C and D/B, and the 90% confidence intervals (CIs) for the ratios were calculated. The lower and upper bounds of the 90% CIs were compared to 80% and 125%, respectively.

Pharmacokinetic Results:

Effect of Heat by Formulation:

First Period of Heat Application (0-10 hours): Mean C_{10} , AUC_{0-10} and AUC_{0-24} values representing the first heat application time period are summarized below for both Duragesic® and D-TRANS® with and without heat.

Mean±SD (CV%) Values for Serum Fentanyl Pharmacokinetic Parameters During the First Period of Heat Application - Effect of Heat By Formulation: Duragesic® and D-TRANS® Fentanyl (n=20)			
	C ₁₀	AUC ₀₋₁₀	AUC ₀₋₂₄
Duragesic® Treatments			
Duragesic® 25 µg/h	0.269±0.16 (58)	0.70±0.54 (78)	5.94±2.45 (41)
Duragesic® 25 µg/h + heat	0.484±0.25 (51)	1.70±0.91 (53)	7.89±3.17 (40)
Duragesic® 25 Heat vs. No Heat			
Log transformed Ratio (90% CI)	181 (147-223)	284 (217-372)	136 (120-154)
D-TRANS® Treatments			
D-TRANS® 25 µg/h	0.380±0.27 (72)	1.26±1.12 (89)	7.45±3.93 (53)
D-TRANS® 25 µg/h + heat	0.559±0.25 (46)	2.18±1.10 (51)	8.57±3.28 (38)
D-TRANS® 25 Heat vs. No Heat			
Log transformed Ratio (90% CI)	161 (131-197)	220 (169-286)	118 (104-134)
Source: Tables 11.1.2.1, 11.1.2.4, 11.1.2.5			
The percent increase in C ₁₀ value upon application of heat was similar for both Duragesic® (181%) and D-TRANS® (161%). For AUC ₀₋₁₀ the percent increase with application of heat was higher for Duragesic® (284%) than for D-TRANS® (220%).			
The intersubject variability in C ₁₀ and AUC ₀₋₁₀ values was high for the "without heat" treatments (58% to 89%) and the variability was somewhat lower for these parameters in the "heat" treatments (46% to 53%).			
<i>Second Period of Heat Application (26-36 hours):</i> The following table summarizes the mean AUC ₂₆₋₃₆ value, which covers the second heat application period together with the overall treatment parameters – C _{max} , AUC ₀₋₇₂ and AUC _{inf} values for both Duragesic® and D-TRANS® with and without heat.			

Mean±SD (CV%) Values for Serum Fentanyl Pharmacokinetic Parameters During the Second Period of Heat Application - Effect of Heat by Formulation: Duragesic® and D-TRANS® Fentanyl (n= 20)				
Treatments	C _{max}	AUC ₂₆₋₃₆	AUC ₀₋₇₂	AUC _{inf}
Duragesic® Treatments				
Duragesic® 25 µg/h	0.691±0.29 (41)	5.15±1.89 (37)	23.9±7.94 (33)	31.2±12.0 (39)
Duragesic® 25 µg/h +heat	0.793±0.22 (28)	6.29±1.65 (26)	27.1±8.93 (33)	35.4±14.1 (40)
Duragesic® 25 µg/h Heat/No Heat				
Log transformed Ratio (90% CI)	122 (109-136)	126 (115-139)	115 (106-125)	114 (105-125)
D-TRANS® Treatments				
D-TRANS® 25 µg/h	0.675±0.27 (40)	5.06±1.84 (36)	24.6±9.79 (40)	32.3±13.1 (41)
D-TRANS® 25 µg/h +heat	0.756±0.27 (36)	5.91±2.02 (34)	27.3±9.80 (36)	34.5±14.3 (42)
D-TRANS® 25 Heat/No Heat				
Log transformed Ratio (90% CI)	111 (100-124)	115 (105-127)	110 (102-119)	103 (94-112)
Source: Tables 11.1.2.2, 11.1.2.4, 11.1.2.5 The AUC ₂₆₋₃₆ values were minimally affected by heat for both formulations. The percent increase with application of heat was 126% and 115% for Duragesic® and D-TRANS® fentanyl, respectively. Consistent with AUC ₀₋₁₀ , the percent increase was slightly higher with Duragesic® compared to D-TRANS®. A similar outcome was seen for the overall C _{max} (percent increase with application of heat of 122% and 111% for Duragesic® and D-TRANS® fentanyl, respectively). Similarly, for the other AUC parameters, AUC ₀₋₇₂ and AUC _{inf} , there was ≤15% increase with application of heat and the 90% confidence intervals for the ratio of the geometric mean AUC parameters were within the 80-125% range.				
<u>Comparison of Heat Treatments with Duragesic® 50 µg/h Treatment:</u> The following tables summarize the data from the "heat" treatments compared with the 50 µg/h Duragesic® treatment. The ratios and 90% confidence intervals are calculated without any dose adjustment.				

Mean±SD (%CV) Pharmacokinetic Parameters - During the First Period of Heat Application: Comparison of Heat Treatments With Duragesic® 50 µg/h Treatment (n=20)			
	C ₁₀	AUC ₀₋₁₀	AUC ₀₋₂₄
Duragesic® Treatments			
Duragesic® 50 µg/h	0.39±0.18 (47)	1.08±0.78 (72)	10.5±3.35 (32)
Duragesic® 25 µg/h + Heat	0.484±0.25 (51)	1.70±0.91 (53)	7.89±3.17 (40)
Duragesic® 25 µg/h Heat / Duragesic® 50 µg/h			
Log transformed Ratio (90% CI)	118 (97-145)	163 (125-212)	73 (64-82)
D-TRANS® Treatment			
D-TRANS® 25 µg/h + Heat	0.559±0.25 (46)	2.18±1.10 (51)	8.57±3.28 (38)
D-TRANS® 25 µg/h Heat / Duragesic® 50 µg/h			
Log transformed Ratio (90% CI)	138 (112-169)	209 (160-272)	77 (68-87)

Source: Tables 11.1.2.1, 11.1.2.4, 11.1.2.6

Mean±SD (%CV) Pharmacokinetic Parameters - During the Second Period of Heat Application: Comparison of Heat Treatments With Duragesic® 50 µg/h Treatment				
	C _{max}	AUC ₂₆₋₃₆	AUC ₀₋₇₂	AUC _{mf}
Duragesic® Treatments				
Duragesic® 50 µg/h	1.19±0.36 (30)	9.25±2.30 (25)	43.4±10.5 (24)	56.9±16.6 (29)
Duragesic® 25 µg/h + Heat	0.793±0.22 (28)	6.29±1.65 (26)	27.1±8.93 (33)	35.4±14.1 (40)
Duragesic® 25 µg/h Heat / Duragesic® 50 µg/h				
Log transformed Ratio (90% CI)	66 (60-74)	67 (61-74)	61 (56-66)	60 (55-66)
D-TRANS® Treatment				
D-TRANS® 25 µg/h + Heat	0.756±0.27 (36)	5.91±2.02 (34)	27.3±9.8 (36)	34.5±14.3 (42)
D-TRANS® 25 µg/h Heat / Duragesic® 50 µg/h				
Log transformed Ratio (90% CI)	60 (54-67)	61 (55-67)	59 (55-64)	56 (52-62)

Source: Tables 11.1.2.2, 11.1.2.4, 11.1.2.6

As seen above, the early exposure parameters (C_{10} and AUC_{0-10}), for both the Duragesic® and D-TRANS® 25 µg/h with heat treatments were higher than that seen with the 50 µg/h Duragesic®. The "with heat" Duragesic® 25 µg/h treatment/Duragesic® 50 µg/h treatment C_{10} and AUC_{0-10} ratios were slightly higher for D-TRANS® 25 µg/h (138% and 209%, respectively) compared with Duragesic® (118% and 163%, respectively).

As expected, the AUC_{26-36} parameter and the overall treatment parameters values (C_{max} , AUC_{0-72} and AUC_{inf}) for both Duragesic® and D-TRANS® 25 µg/h with heat treatments were close to 50% of the respective Duragesic® 50 µg/h parameter values. These results are consistent with the minimal effect of heat observed during the second period of heat application between 26-36 hours for both D-TRANS® and Duragesic® 25 µg/h treatments.

Skin Temperatures:

The skin temperature profile was similar for the two "heat" treatments. It was also similar for the three "without heat" treatments.

System Functionality Results:

Most (≥91.7%) D-TRANS® fentanyl 25 µg/h systems were adhered to at least 90% of the application-site area at each assessment time. All (100%) non-heat treated D-TRANS® fentanyl 25 µg/h systems were adhered to 90% or more of the application-site area 24 and 36 hours after application.

Most (≥72.7%) Duragesic® fentanyl 50 µg/h systems were adhered to at least 90% or more of the application-site area at each assessment time. Fewer Duragesic® 25 µg/h systems were adhered to 90% or more (81% in both the with and without heat treatments) of the application-site area compared with D-TRANS® fentanyl 25 µg/h systems.

Safety Results: No serious AEs (SAEs) were reported during this study. One subject was withdrawn from the study prematurely because of adverse events of mild nausea and mild to moderate vomiting, considered possibly related to treatment by the investigator. Another subject was withdrawn from the study because of a positive pregnancy test. The number of subjects reporting at least one AE was comparable between the following matching treatment categories: Duragesic® 25 µg/h (no heat) and D-TRANS® 25 µg/h (no heat): 5 (23%) and 3 (14%), respectively; Duragesic® 25 µg/h with heat and D-TRANS® 25 µg/h with heat: 6 (29%) and 6 (25%), respectively; and Duragesic® 50 µg/h was comparable with both Duragesic® and D-TRANS® 25 µg/h with heat: 6 (27%) compared with 6 (29%) and 6 (25%), respectively. Overall, more subjects reported adverse events during treatment with heat compared with normal treatment for both Duragesic® 25 µg/h fentanyl and D-TRANS® 25 µg/h fentanyl. Adverse events reported in ≥2 subjects were headache, increased libido, and nausea. Of these, drug-related AEs included headache and nausea. Other adverse events considered related to study treatment (Duragesic® and/or D-TRANS® fentanyl) by the investigator were tachycardia, vomiting, abdominal pain, and stomach ache.

No subject reported an application-site reaction during the study. No topical AEs were reported at the 24-hour post-system removal assessment. At the 1-hour post-system removal assessment, most topical AEs were mild.

Overall, there were no clinically significant changes from baseline in vital signs, clinical laboratory tests, and physical examination and ECG findings for this study population.

Conclusions:

The new formulation D-TRANS[®] fentanyl matrix system, differs from the marketed formulation Duragesic[®] in that it is a matrix structure and has no rate control membrane and no skin-permeation enhancer. The results from this study indicate that application of heat had similar effect on the serum fentanyl concentration for both Duragesic[®] and D-TRANS[®] fentanyl 25 µg/h treatments. For both formulations application of heat during the first 10 hours increased fentanyl exposure by 2-3 fold and application of heat between 26-36 hours when fentanyl concentrations were almost at steady state, had minimal affect. The increase in fentanyl exposure between 0-10 hours when heat was applied on Duragesic[®] and D-TRANS[®] fentanyl 25µg/h systems was significantly higher than Duragesic[®] 50 µg/h at twice the dose.

No SAEs were reported. Most AEs were of mild severity, none were severe. The systemic and topical safety profiles were similar for the treatment groups, and no new safety issues were identified with any treatment.

Date of the report: 03 September 2004

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/s/

Rajnikanth Madabushi
7/17/2009 01:38:32 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/17/2009 04:43:19 PM
BIOPHARMACEUTICS

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	19813/SCF-044
Submission Date:	1/30/2009, 4/10/2009, 4/28/2009
Brand Name:	DURAGESIC
Generic Name:	Fentanyl transdermal system
Formulation:	Transdermal patch
Strength:	12, 25, 50, 75 and 100 µg/h
Sponsor:	J&J
Reviewer:	John Duan, Ph.D.
Submission Type:	Revised formulation

INTRODUCTION

The subject of this NDA supplement is a new formulation for transdermal delivery of fentanyl.

The sponsor has developed a transdermal fentanyl matrix system (D-TRANS), which is currently marketed outside the US under the international trade name DUROGESIC. The drug content and size (surface area) of each dosage strength of the proposed product are provided in the following table.

Dosage Strength, µg/h	Target Drug Content, mg	Active Area, cm ²
12	2.1	5.25
25	4.2	10.5
50	8.4	21.0
75	12.6	31.5
100	16.8	42.0

THE COMPOSITION OF THE NEW FORMUALTION

The D-TRANS® fentanyl matrix system is a translucent, rectangular transdermal patch. It is a drug-in-adhesive formulation designed to release fentanyl continuously for 72 hours after application to intact skin. There are 5 dosage strengths for D-TRANS® fentanyl delivery: 12 µg/h (R004263-F904), 25 µg/h (R004263-F900), 50 µg/h (R004263-F901), 75 µg/h (R004263-F902), and 100 µg/h (R004263-F903). The lowest dose is referred to as 12 µg/h even though it is exactly half of the 25 µg/h strength (12-1/2 µg/h). Each patch is intended to be worn for 3 days. All dosage strengths of D-TRANS® fentanyl are manufactured using the same formulation. The various dosage strengths are achieved by varying the size, or surface area, of each system (5.25 cm², 10.5 cm², 21.0 cm², 31.5 cm², and 42.0 cm², respectively).

The following table presents the quantitative composition in mg per unit dose (mg/patch) of D-TRANS® fentanyl.

Quantity Per Patch (mg per patch)					
Nominal Delivery Rate:		12 µg/h	25 µg/h	50 µg/h	75 µg/h
Patch Area (cm ²):		5.25	10.5	21.0	31.5
Components	Function	Quality Standard			
Backing Layer ^a	(b) (4)				
Drug Reservoir					
Protective Liner ^a					
Inks					
Total Patch Weight		(b) (4)			
PATCH WEIGHT WITHOUT PROTECTIVE LINER		(b) (4)			

^a Weights shown are examples. Material added to batch as (b) (4)

^b Dry weight

^c Removed during processing

^d (b) (4)

^e

^f

A comparison between the proposed new formulation and approved formulation is shown in the following table.

Attribute	DURAGESIC [®] reservoir patch	D-TRANS [®] fentanyl matrix
Dosage Strengths	12, 25, 50, 75, and 100 µg/h	12, 25, 50, 75, and 100 µg/h
Rate Control	(b) (4)	
Construction		
Backing		
Backing Printing Ink		
Drug Layer		
Adhesive		
Oversized Protective Liner		

In a Type A meeting briefing package dated May 9, 2008, it was proposed that 1) D-TRANS fentanyl matrix formulation be submitted as a prior approval CMC supplemental new drug application (PAS); 2) that since the drug substance was not changing, the sNDA would include information on matrix drug product only; 3) that the PAS would include three months of stability data from one lot of D-TRANS used to produce all strengths and supporting stability data (thirty-six months data at 25°C/60%RH and 30°C/65%RH and six months at accelerated conditions 40°C/75%RH); 4) that a bioequivalent study, FEN-PAI-1019, would be conducted and study report included in the PAS.

BIOEQUIVALENCE STUDIES

Two biopharmaceutic studies are included and summarized in support of this submission. Study FEN-PAI-1019 a pivotal bioequivalence study conducted to evaluate the pharmacokinetics (PK) of the D-TRANS fentanyl matrix system to the US approved DURAGESIC fentanyl reservoir system at the highest dose strength of 100 µg/h.

Study C-2003-038 a bioequivalence study originally conducted to support the 2004 international filings of the 12.5 µg/h D-TRANS fentanyl matrix system. This study is included as supportive information for this submission.

A tabular listing of products used in the biopharmaceutics studies in support of the D-TRANS matrix system is presented below.

Clinical Study	Formulation	Dosage Strength	Duration of Dosing	Code #/ Control #
	Pivotal Study			
FEN-PAI-1019	D-TRANS (Fentanyl matrix system)	100 µg/h	72 h single application	0823429
	DURAGESIC (Fentanyl reservoir system -US)	100 µg/h	72 h single application	0815899
	Supportive Study			
C-2003-038	D-TRANS (Fentanyl matrix systems)	4 x 12.5 µg/h	72 h single applications	0012975/0223243
	DUROGESIC™ (Fentanyl reservoir system ex-US)	2 x 25 µg/h	72 h single applications	03EB886
	D-TRANS (Fentanyl matrix system)	1 x 50 µg/h	72 h single applications	0012977/0223249
	Additional Studies			
C-2002-046	DUROGESIC™ (Fentanyl reservoir system ex-US)	100 µg/h	72 h single applications	02GB361
	D-TRANS (Fentanyl matrix system)	100 µg/h	72 h single applications	0013167/0300817
C-2002-049	DUROGESIC™ (Fentanyl reservoir system ex-US)	100 µg/h	288 h as 4 consecutive systems each worn for 72 h during each treatment	02JB409
	D-TRANS (Fentanyl matrix system)	100 µg/h	288 h as 4 consecutive systems each worn for 72 h during each treatment	0012979/0223257

The study synopsis of study FEN-PAI-1019 and the reviewer's analysis for this bioequivalence study are presented in the Appendix. Both results show that the D-TRANS (Fentanyl matrix system) and the DURAGESIC (Fentanyl reservoir system -US) are bioequivalent.

RELEASE TEST AND SPECIFICATION

(b) (4)

The determination of the in vitro drug release of fentanyl from D-TRANS® fentanyl matrix systems

Method Parameter	Explanation/Justification
Apparatus	Standard USP <724> Type 7 Bath
Media Volume	Release media volume per sample of each strength of Duragesic Matrix systems is set (varying from 150 mL to 250 mL) to bracket the validated fentanyl assay linearity range.
Bath Temperature	$32 \pm 0.3^{\circ}\text{C}$. Current USP<724> Apparatus 7 allows $32 \pm 0.5^{\circ}\text{C}$.
Agitation Speed and amplitude	ALZA calibrated the agitation speed to 30 cycles per minute with an amplitude of about 2 cm following USP<724> Apparatus 7 monograph.
Sample Holder	The reciprocating holder is the cylinder option as described in current USP<724> Apparatus 7 monograph with (b) (4) used to secure the nylon netting and transdermal systems.
Release Media	(b) (4)

As shown in the above table, the method involves attaching the active system to a suitable holder as described in USP <724> Apparatus 7. The system/holder assembly is then attached to a mechanical shaker and is continuously immersed while being agitated (b) (4)

The proposed drug release specification is listed in the following table.

Release interval	Method	Conforms to USP <724> Acceptance Table 1
(b) (4)		

THE JUSTIFICATION FOR THE RELEASE TEST AND SPECIFICATIONS

The acceptance criteria for each drug release time interval is based on $\pm$ (b) (4) % of target. The acceptance criteria for each time interval are tighter than those for the current DURAGESIC® reservoir specification. Fentanyl release will be specified in mg/cm² for direct comparison between various system sizes (doses) on a unit area basis.

Selection of Drug Release Intervals

For DURAGESIC® reservoir system, the release rate is currently specified at intervals (b) (4) hours; whereas DURAGESIC matrix (b) (4)

The currently approved product, DURAGESIC® (fentanyl transdermal system) is a form, fill and seal patch with a fentanyl gel as the drug reservoir and a rate-controlling membrane. The proposed formulation, D-TRANS® fentanyl matrix system (D-TRANS® fentanyl) is a drug-in-adhesive matrix design. (b) (4)

The drug release time points selected for D-TRANS® fentanyl are based on the characteristic profile of drug release for a matrix system and the need for an adequate number of time points for a descriptive release profile and analytical method (HPLC) sensitivity and precision. This procedure uses an indexing type instrument, USP <724>, Type 7. As the number of time points increases the total drug released per time point decreases, thus increasing analytical variability, especially for the smaller system sizes. (b) (4)

Since the (b) (4) did not incorporate any formulation or process changes, the data derived from the 2002/2003/2004 timeframe are appropriate for use in this assessment. A capability analysis of lot clearance fentanyl release data for all system sizes from the registration lots, as well as the previous lots, was performed against the acceptance criteria used to release the registration lots. The limits of the acceptance criteria are (b) (4) % of target release at each interval.

The following table shows the release results from the batch analysis.

Time intervals	Acceptance Criteria	12 µg/h system	25 µg/h system	50 µg/h system	75 µg/h system	100 µg/h system
----------------	---------------------	-------------------	-------------------	-------------------	-------------------	--------------------

(b) (4)

Discriminatory properties of the drug-release method

The drug release method was developed based on the sponsor's prior experience with transdermal products in general, and fentanyl transdermal products in particular. The total drug loading in the adhesive layer is determined by the content assay procedure and the results are expressed in terms of mg fentanyl/system. Because the content assay only measures total fentanyl content, the content assay method cannot distinguish differences in drug concentration that might be offset by differences in the thickness of the drug-in-adhesive layer. The drug release method can distinguish these differences in drug layer thickness and drug concentration, which are important to product bioavailability. Therefore, the drug release method provides a discriminative power that is complementary to the assay method for quality control purposes. However, an in vitro/in vivo correlation is not available and cannot be provided for D-TRANS® fentanyl.

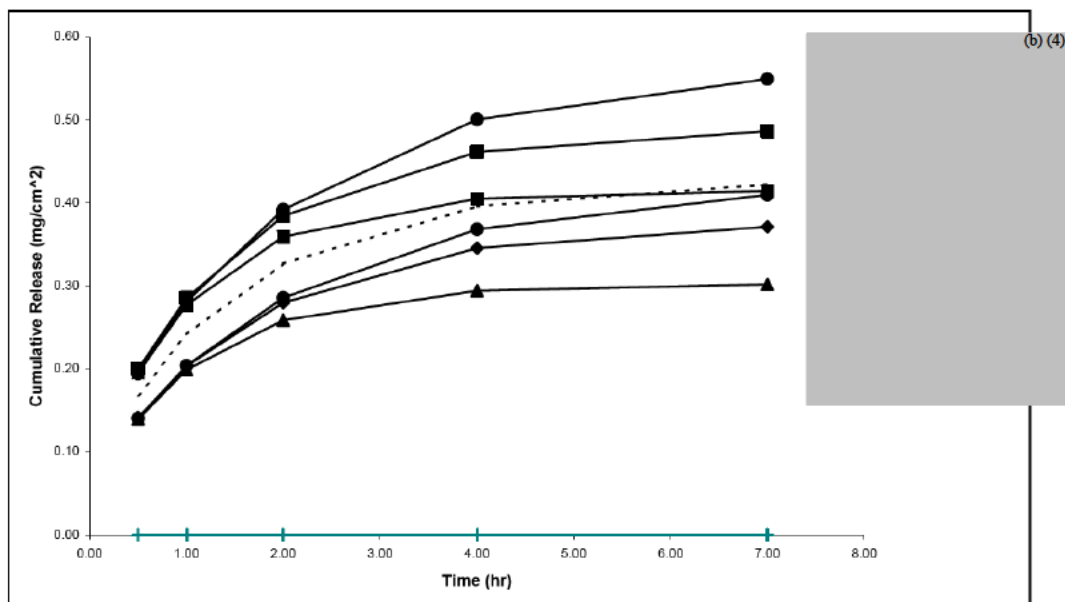
Experiments were conducted to demonstrate that the drug release method is capable of distinguishing differences in drug layer thickness and/or differences in drug concentration when the total drug loading cannot be distinguished by the drug assay.

Six 42 cm² size transdermal systems were prepared containing two different concentrations of fentanyl (b) (4) at three different thicknesses (b) (4) r (b) (4) or corresponding to (b) (4), respectively, as shown Table below). Two of the 6 systems contained essentially the same drug loading (System 4 with (b) (4) mg, and System 5 with (b) (4) mg, calculated) but different drug concentrations and drug layer thicknesses. The two off-target concentrations of fentanyl (b) (4) and the two

off-target thicknesses (b) (4) represented 85% and 115% of the respective target levels. The cumulative amount of fentanyl released was measured as a function of time at 5 time intervals up to 7 hours at 32 °C. The figure below shows the fentanyl release profiles for Systems 1 to 6.

Table. Transdermal Fentanyl Systems Prepared to Demonstrate the Discriminating Nature of the Drug-Release Method

System	Fentanyl Concentration (% w/w)	Reservoir Thickness (mil)/(μm)	Theoretical Drug Loading (mg/unit)
--------	--------------------------------	--------------------------------	------------------------------------



* Note: The dotted line represents the median.

The figure shows that at the 32°C test condition used in the drug release, the test can distinguish systems containing different concentrations of drug in the first few hours of release, especially for systems 4 and 5, for which the total drug loading is about identical. After approximately 4 hours, the discriminatory power for drug concentration diminishes and shifts to total drug loading discrimination where the assay method will provide adequate discriminative power.

Establishing criteria for each drug release interval

Specifications for drug release are based on defining drug release intervals and tolerances for each interval. The justification for choosing drug release intervals is based on four intervals representing approximately (b) (4) % of total drug release.

Tolerances for each drug release interval were assigned in accordance with ICH guidance for setting specifications, taking into account the following results:

- Results of Clinical Studies (PK and Bioequivalence)
- Accelerated and Long-term Stability Studies
- Analytical and Manufacturing Variability

The specifications were evaluated with respect to pharmacopoeial standards. USP <724> Level 1 and Level 2 drug release specifications are shown in Table 3.

Evaluation of specifications relative to clinical studies

Pharmacokinetic and bioequivalence studies were conducted during the product development phase, and are representative of the commercial product and processes. The average values for each drug release interval are presented in the following table.

Study No.	Item Number / Lot ID	Description	Dosage, mcg/h	Avg. Drug Release, mcg/cm ²			
				0-0.5 h	0-2 h	0-4 h	0-24 h
C-2002-048	0012976/0223247	PK Study	25	0.15	0.31	0.38	0.42
C-2002-048	0012977/0223250	PK Study	50	0.15	0.30	0.38	0.41
C-2002-048	0012978/0223253	PK Study	75	0.15	0.30	0.38	0.42
C-2002-048	0012979/0223257	PK Study	100	0.15	0.30	0.38	0.42
C-2002-047	0013167/0300817	PK Study	100	0.15	0.31	0.38	0.41
C-2003-038	0012975/0223243	BE Study	12.5	0.16	0.31	0.37	0.40
C-2003-038	0012977/0223249	BE Study	50	0.15	0.30	0.37	0.40
C-2002-046	0013167/0300817	BE Study	100	0.15	0.31	0.38	0.41
C-2002-049	0012979/0223257	BE Study	100	0.15	0.30	0.38	0.42
FEN-PAI-1019	0017700/0823429	BE Study	100	0.15	0.30	0.37	0.40

The minimum and maximum drug release for individual samples at each interval is shown in the table below. Drug release data from each of these studies is in accordance with the proposed specifications.

Dosage	0-0.5 h		0-2 h		0-4 h		0-24 h	
	Min	Max	Min	Max	Min	Max	Min	Max
12.5	(b) (4)							
25								
50								
75								
100								

Evaluation of specifications relative to accelerated and long-term stability

An evaluation of all data, including accelerated and long-term stability results, was conducted to understand the variability introduced over the 24 month proposed expiration

date. With the exception of a single data point for the 25mcg/h dosage at the 0-0.5 h drug release interval, all data were within the Level 1 USP <724> criteria. The minimum and maximum values observed for each dosage and drug release interval are presented in the following table.

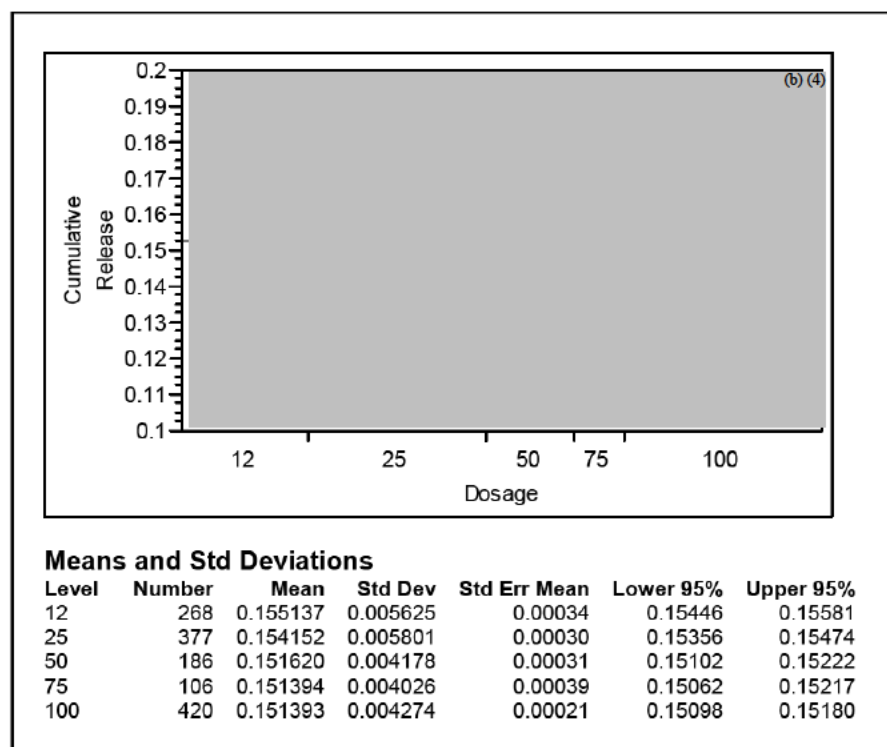
Dosage	0-0.5 h		0-2 h		0-4 h		0-24 h	
	Min	Max	Min	Max	Min	Max	Min	Max
12.5	(b) (4)							
25								
50								
75								
100								

Evaluation of Analytical and Manufacturing Variability

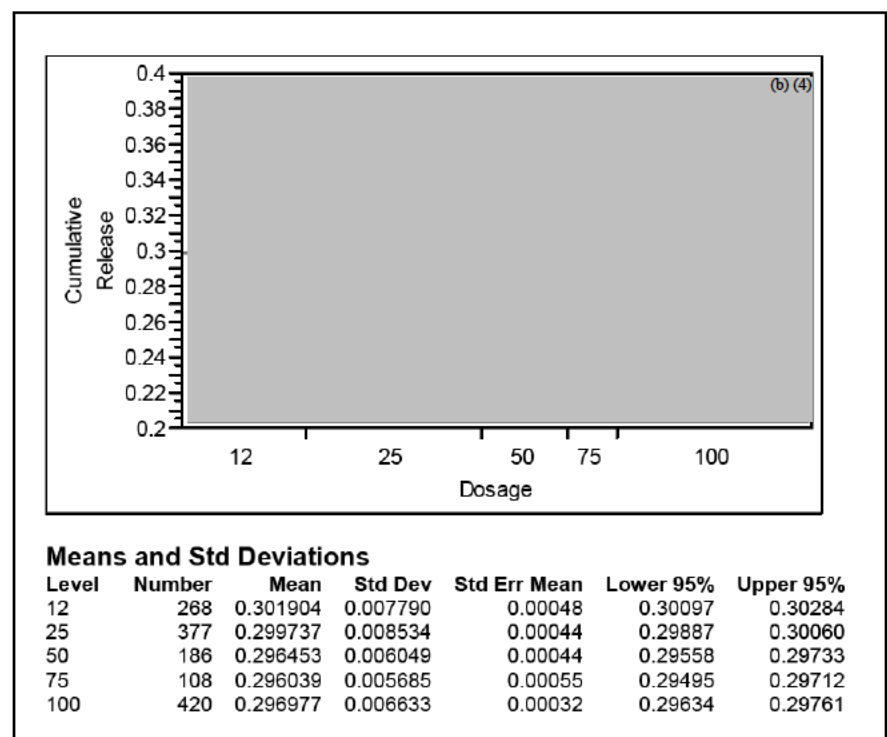
All of the raw data generated from the clinical and commercial batches that were placed on accelerated and long-term stability were evaluated with respect to analytical and manufacturing variability. The data was evaluated against the proposed specification ranges to determine the process capability of meeting the criteria. The table below shows the capability and sigma levels with respect to Level 1 USP <724> criteria for each drug release interval.

Drug Release Interval	0 – 0.5 h	0 – 2 h	0 – 4 h	0 – 24 h
Process Capability Index, Cpk	(b) (4)			
Sigma Quality				

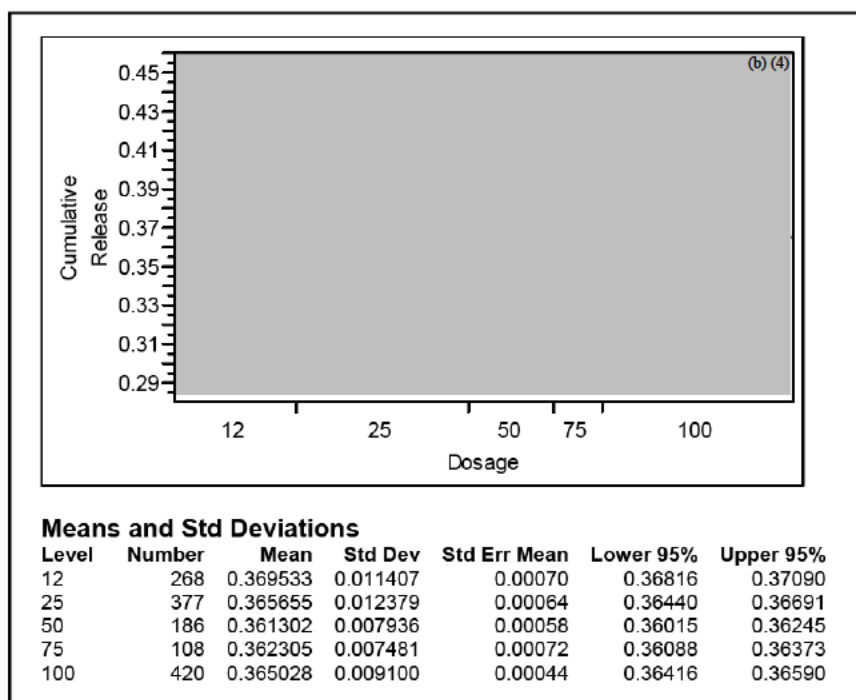
The following figures show a comparison of each dosage with respect to the cumulative release of drug ($\mu\text{g}/\text{cm}^2$). The results verify that each dosage has comparable drug release for each interval.



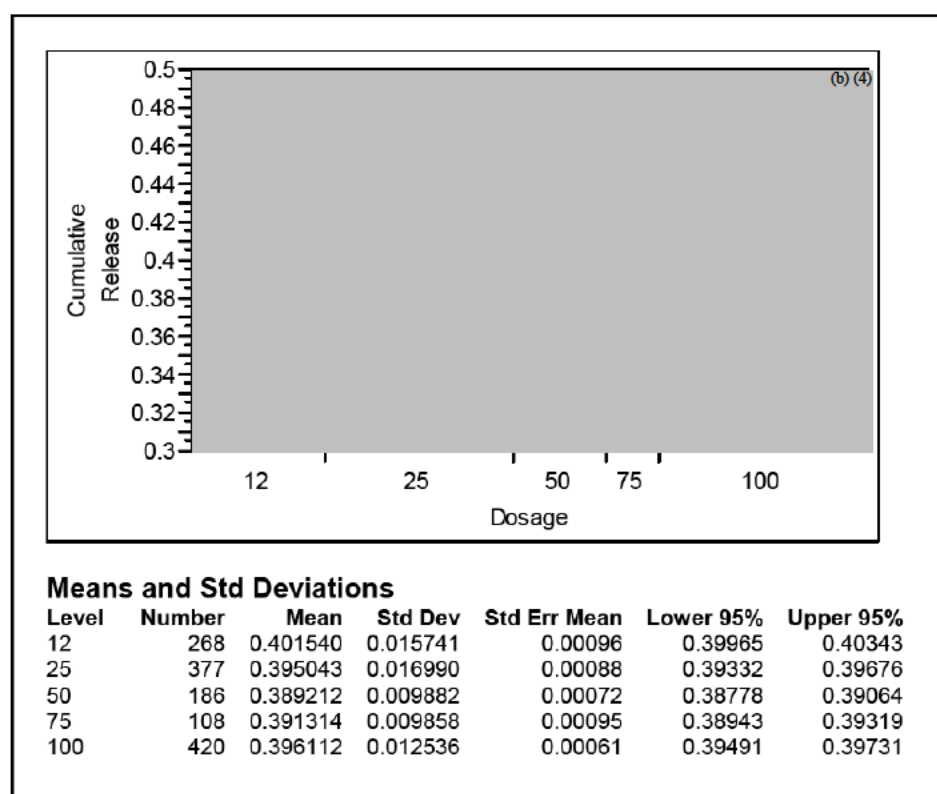
Oneway Analysis of Cumulative Release By Dosage Drug Release Interval=0-0.5 hr



Oneway Analysis of Cumulative Release by Dosage Drug Release Interval 0-2 hr



Oneway Analysis of Cumulative Release by Dosage Drug Release Interval 0-4 hr



Oneway Analysis of Cumulative Release by Dosage Drug Release Interval 0-24 hr

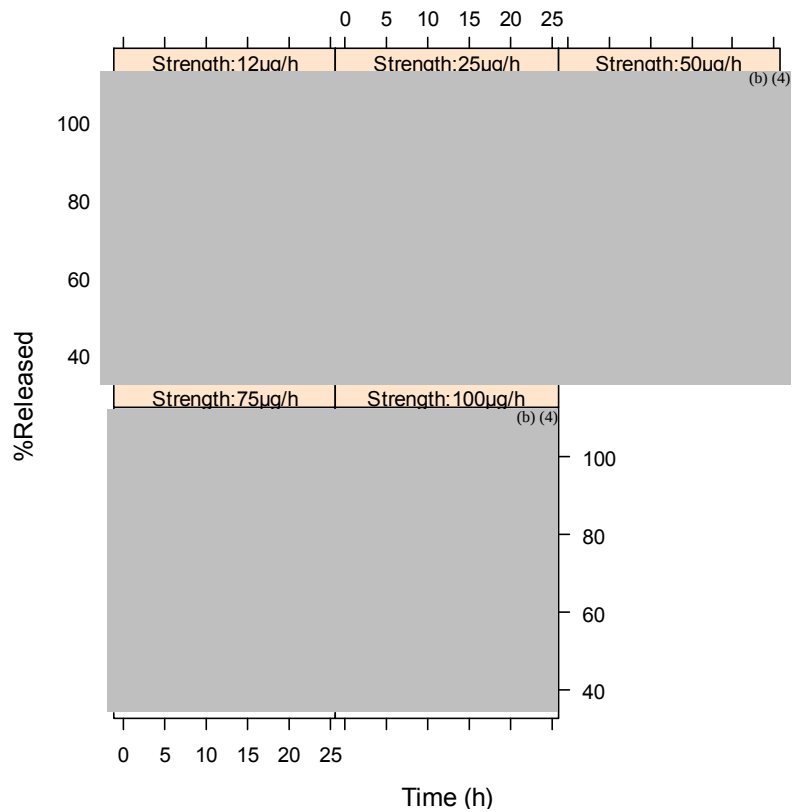
Raw Data and Confirmation that the Data Performs as Expected

The drug release data, including Clinical, Registration, and 2004 Process Validation Batches are submitted. The drug release data for each dosage and interval is normalized to mg/cm^2 , to allow pooling for data analysis. For each data set and drug release interval, the average % release was also calculated and is shown. These correspond to the predicted drug release intervals of (b) (4) (0 – 0.5h interval), (b) (4) (0-2h interval), (b) (4) (0-4h interval), and (b) (4) (0-24h interval). The following table shows the relationship between release interval, acceptance criteria, and % drug release (relative to the specification).

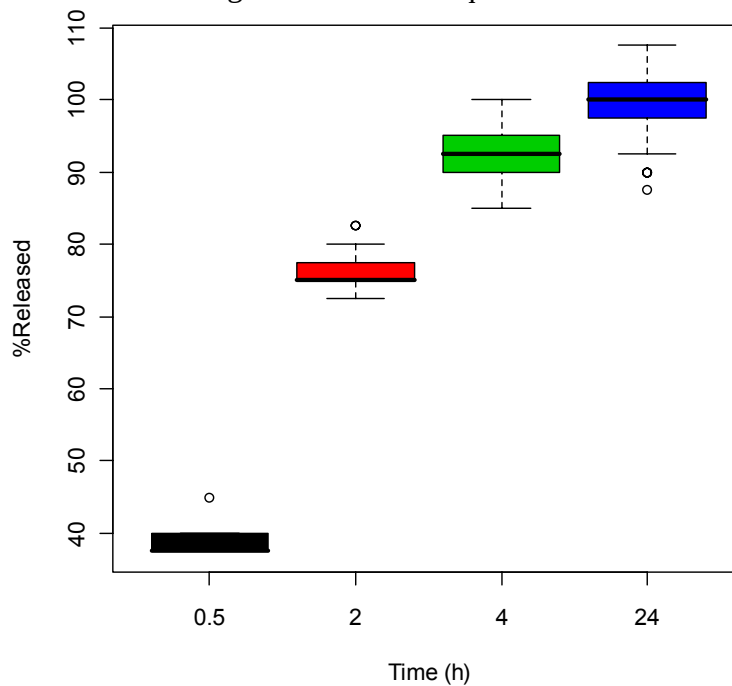
Test Parameter	Acceptance Criteria (Level 1)	% Drug Release (Target, Relative Specification)
Drug Release	Conforms to USP <724> Acceptance Table 1	
1. 0 – 0.5 h interval	(b) (4)	
2. 0 – 2 h interval		
3. 0 – 4 h interval		
4. 0 – 24 h interval		

COMMENTS

1. During the review process, we conveyed the following comments to the sponsor. The requested information has been evaluated in this review. For completeness, they are recorded below.
 - The details of the release test method, including the apparatus, the medium, the volume, the agitation speed, and other conditions with appropriate justification for each condition. For example, please list all the media you have used and justify why the current medium is proposed. Other conditions should be justified in the similar fashion as appropriate.
 - The detailed justification for the proposed release specifications. The justifications for release specifications included in the submission are not appropriate. Please include the release data for each strength with all available data and explain how the specifications were chosen.
 - All raw data and detailed data analysis results should be included.
2. The proposed release specifications are not adequate (too wide). The following figure shows the Reviewer's analyses which indicate the release profiles among different strengths are similar. There are release data of 43 batches for a total of 1512 units, including 240 units for 12 $\mu\text{g}/\text{h}$ strength, 288 units for 25 $\mu\text{g}/\text{h}$ strength, 288 units for 50 $\mu\text{g}/\text{h}$ strength, 312 units for 12 $\mu\text{g}/\text{h}$ strength, and 384 units for 100 $\mu\text{g}/\text{h}$ strength. In the Reviewer's analyses, percentage released data are used instead of amount.



As seen, most data points are overlapped. Therefore, the release data for different strength are pooled together to calculate the statistics at each time point. As shown in the following figure, the distributions of the release data at every time point are narrow and few data points are out of the range of 1.5 times of quartiles.



The following table shows the statistics for the pooled data at each time point. The percent released are shown with the amount ($\mu\text{g}/\text{cm}^2$) in parentheses.

Time (h)	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD
0.5	37.5 (0.15)	37.5 (0.15)	37.5 (0.15)	38.35 (0.15)	40 (0.16)	45 (0.18)	1.226 (0.0049)
2	72.5 (0.29)	75 (0.30)	75 (0.30)	75.48 (0.30)	77.5 (0.31)	82.5 (0.33)	1.693 (0.0068)
4	85 (0.34)	90 (0.36)	92.5 (0.37)	92.43 (0.37)	95 (0.38)	100 (0.40)	2.404 (0.0096)
24	87.5 (0.35)	97.5 (0.39)	100 (0.40)	99.81 (0.40)	102.5 (0.41)	107.5 (0.43)	3.394 (0.0136)

Based on these observations, the following release specification is recommended.

Release interval	%Released (release amount)
Conforms to USP <724> Acceptance Table 1	
0 - 0.5 h	30-45 (0.12 – 0.18 mg/cm^2)
0 - 2 h	65-85 (0.26 – 0.34 mg/cm^2)
0 - 4 h	82-102 (0.33 – 0.41 mg/cm^2)
0 - 24 h	90-110 (0.36 – 0.44 mg/cm^2)

- The bioequivalence study is considered to be adequate and the equivalence between the proposed product and approved product has been established.

RECOMMENDATION

The bioequivalence between the proposed product and approved product has been established. The release specifications are recommended as the table in Comments. Please convey the comments and the recommendations to the review chemists and to the applicant as appropriate.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

cc: NDA 19813
Patrick Marroum, John Duan

APPENDIX. Study synopsis from the sponsor and the reviewer's analysis

SYNOPSIS

Issue Date: 27 January 2009

Document No.: EDMS-PSDB-9403478:2.0

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development
<u>Name of Finished Product</u>	DURAGESIC®
<u>Name of Active Ingredient(s)</u>	Fentanyl

Protocol No.: FEN-PAI-1019

Title of Study: A Pivotal Bioequivalence Study Assessing Transdermal D-TRANS Fentanyl 100 µg/h Matrix System to DURAGESIC® Fentanyl 100 µg/h Reservoir System After Single Application in Healthy Subjects.

Principal Investigator: Michelle Ababa, M.D.

Publication (Reference): None.

Study Period: 26 September 2008 to 1 December 2008.

Phase of Development: Phase 1

Objectives: to evaluate the bioequivalence of D-TRANS fentanyl 100 µg/h matrix system to DURAGESIC fentanyl 100 µg/h reservoir system after single application in healthy subjects. Additionally, safety of the subjects was evaluated throughout the study.

Methods: This was a single-center, randomized, open-label, single application, 2-period crossover study in healthy adult subjects. All screening procedures were performed to determine eligibility within 21 days before admission to the research facility. After satisfactorily completing the naloxone challenge test on Day -1 of Period 1, subjects who met the selection criteria were randomly assigned to 1 of the 2 treatment sequences: Treatment Sequence 1 (AB) or Treatment Sequence 2 (BA).

- Treatment A: DURAGESIC 100 µg/h reservoir system applied for 72 hours
- Treatment B: D-TRANS 100 µg/h matrix system applied for 72 hours

Each system was worn on the lateral aspect of upper, outer arm. The treatment received during Period 2 was placed on the contra-lateral arm. Successive treatment periods were separated by a washout period of 8 to 14 days. Subjects remained at the study site from Day -1 until completion of the 120-hour postdose pharmacokinetic blood sample collection on Day 6 of each treatment period. During this study 2 opioid antagonists were used:

- Naltrexone hydrochloride tablets to continuously block the effect of fentanyl delivered through the DURAGESIC and D-TRANS systems; and
- Naloxone hydrochloride injectable that was used for the opioid challenge test performed on Day -1 of Period 1, and as a rescue medication if required.

Number of Subjects (planned and analyzed): Ninety-one healthy men or women were enrolled so that 74 subjects completed both treatment periods and provided pharmacokinetic data for both DURAGESIC and D-TRANS systems.

Diagnosis and Main Criteria for Inclusion: Healthy men or women between 18 to 55 years of age, inclusive with body mass index between 18 to 30 kg/m² at screening; no clinically relevant abnormalities as determined by: medical history, physical examination, vital signs, blood chemistry, complete blood count, urinalysis, and electrocardiogram; negative naloxone challenge test; negative urine drug test and alcohol test at screening and 24 hours before start of treatment initiation in each treatment period; subjects were to

utilize a medically acceptable method of contraception throughout the entire study period including the washout period and for 3 months (men) or 1 week (women) after the study was completed.

Test Product, Dose and Mode of Administration, Batch No.: D-TRANS fentanyl 100 µg/h matrix system applied to the lateral aspect of the subject's upper arm for 72 hours. Lot No.: A06374-001L02, Package Lot Number: T94935, Expiration date: 08/2010.

Reference Therapy, Dose and Mode of Administration, Batch No.: DURAGESIC fentanyl 100 µg/h reservoir system applied to the lateral aspect of the subject's upper arm for 72 hours. Lot No.: A06374-001L01, Package Lot Number: T94934, Expiration date: 06/2010.

Commercially available naltrexone and naloxone were provided by the site. Naloxone: Lot No.: 65-343-EV, 52-111-EV (expiration date: 05/2010, and 04/2009, respectively). Naltrexone: Lot No.: 170L62812, 1170L60943, and 1170M66473 (expiration date: 09/2009, 03/2009, and 05/2010 respectively).

Duration of Treatment: was approximately 28 days (two 7-day treatment periods and one ≤14 day washout period between dose administration). The screening period was to be completed within 21 days before Check-in for Period 1.

Criteria for Evaluation:

Pharmacokinetic Evaluations: During each treatment period, serial blood samples were collected before and for 120 hours following the initiation of each treatment. Both the D-TRANS and DURAGESIC transdermal systems were applied to each subject for 72 hours, 1 system per treatment period. The following key serum pharmacokinetic parameters were calculated: C_{max} , t_{max} , AUC_{last} , AUC_{∞} , $t_{1/2}$, and λ_z .

Skin Assessments: The skin site to which D-TRANS and DURAGESIC transdermal systems were applied was monitored for the development of topical adverse events (AEs) (erythema, edema, papules, pustules, and itching) at 1 and 24 hours after removal of each system.

System Functionality: Assessments of system adherence occurred each time vital signs were collected. Additionally adherence scores of the systems were recorded at 24, 48, and 72 hours post system application.

Safety Assessments: Safety was evaluated by examining the incidence and type of AEs, skin assessments at the application sites (after removal of the systems), and changes in clinical laboratory test values, physical examination results, vital signs, pulse oximetry measurements, and sleeping respirations from the screening phase through study completion, including the washout interval.

Statistical Methods:

Sample size: Using an estimate of 20% for intrasubject coefficient of variation (CV) for AUCs and C_{max} , a sample size of 74 subjects was sufficient to conclude the bioequivalence (confidence intervals of the geometric mean to fall within 80% to 125%) of the D-TRANS matrix system and the DURAGESIC reservoir system with a power of 80% when the true ratio of the means of the 2 products was equal to 115%. Ninety-one subjects enrolled in the study and 74 subjects completed all assigned treatments.

Pharmacokinetic Analysis: Mixed-effects models were fitted to the data with the logarithm of AUCs and C_{max} as the dependent variables, treatment-sequence group, period, and treatment (A and B) as fixed effects, and subject as a random effect. The estimated least square means and intrasubject variance from the mixed-effects model was used to construct 90% confidence intervals for the differences in means on a log scale between D-TRANS and DURAGESIC. The limits of the confidence intervals were retransformed using anti-logarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters of treatment B versus A.

Safety Analysis: All subjects who received study medication were included in the safety evaluation. Early termination data, AEs, vital signs, concomitant medications and laboratory data were listed.

RESULTS:

Of the 91 randomized subjects, 74 (81%) completed the study. Of the 17 withdrawn subjects, 1 due to AEs, 1 due to pregnancy, 11 withdrew consent, and 4 were withdrawn due to other reasons. Of the 91 randomized subjects, 50 were men and 41 were women. For both sequences, the mean age and the BMI were comparable and within specified study criteria.

PHARMACOKINETIC RESULTS: The systemic exposure of fentanyl (as measured by serum C_{max} and AUC values) and the time to reach maximum fentanyl concentrations (t_{max}) were comparable across treatments. The mean half-life values ranged between 26 and 27 hours for both treatments.

Mean ($\pm$ SD) Serum Fentanyl Pharmacokinetic Parameters After a Single Application of both the DURAGESIC (Reservoir) and D-TRANS (Matrix) Fentanyl 100 μ g/hr Systems
(Pharmacokinetic Analysis Set)

Treatment	D-TRANS 100 μ g/hr (Test)			DURAGESIC 100 μ g/hr (Reference)		
PK Parameters	n	Mean $\pm$ SD	%CV	n	Mean $\pm$ SD	%CV
C_{max} (ng/mL)	79	2.39 $\pm$ 1.07	45.0	81	2.30 $\pm$ 0.83	35.9
t_{max} (h)*	79	42.0 (8.0 – 78.0)	--	81	42.0 (18.0 – 78.0)	--
AUC _{last} (ng•h/mL)	79	147 $\pm$ 53.9	36.7	81	136 $\pm$ 40.8	30.0
AUC _{∞} (ng•h/mL)	79	167 $\pm$ 63.6	38.2	81	155 $\pm$ 52.4	33.7
$t_{1/2}$ (h)	79	26.9 $\pm$ 8.9	33.3	81	26.0 $\pm$ 9.1	34.9

* t_{max} reported as median (min – max)

The estimated ratio of mean pharmacokinetic parameters of fentanyl and 90% CIs of the pharmacokinetic parameters of fentanyl are presented in the table below. The ratio of the geometric means between the DURAGESIC and D-TRANS treatments for C_{max} , AUC_{last}, and AUC _{∞} , were 105.83%, 109.96%, and 109.71%, respectively. The 90% CIs of the ratios of the geometric means for all fentanyl PK parameters were contained within the bioequivalence criteria of 80% to 125%.

Estimated ratio of geometric means and 90% confidence intervals for the Ratio Between the DURAGESIC (Reservoir) and D-TRANS (Matrix) Fentanyl 100 μ g/hr Systems
(Statistical Analysis Set)

PK Parameter	Intra-subject CV (%)	Geometric Means		90% Confidence Intervals		
		D-TRANS 100 μ g/hr (Test)	DURAGESIC 100 μ g/hr (Reference)	Ratio (Test/Ref, %)	Lower limit (%)	Upper limit (%)
C_{max} (ng/mL)	18.7	2.26	2.13	105.83	100.58	111.36
AUC _{last} (ng•h/mL)	13.0	141.60	128.77	109.96	106.14	113.92
AUC _{∞} (ng•h/mL)	14.3	159.92	145.76	109.71	105.51	114.08

N=74

SYSTEM FUNCTIONALITY: All systems were adhered to $\geq$ 75% of the application-site area with no edges unattached for the 72-hour-wearing period. The D-TRANS system had a greater percentage of subjects with $\geq$ 90% adherence than the DURAGESIC system in both periods at all time points.

SAFETY RESULTS: No death or serious AEs were reported. The AEs reported in this study were: 18 (22%) during D-TRANS treatment and 17 (20%) during DURAGESIC treatment. AEs were all of mild to moderate severity. One subjects discontinued due to AEs (vomiting) considered mild, and possibly related to the study. The most common AEs in this study ($>$ 5% of subjects in either group) vomiting, headache and nausea, occurred with both treatments and are known effects of fentanyl and naltrexone. No changes in clinical laboratory test results or vital signs were considered clinically significant.

Five subjects had application site reactions (ASRs) recorded based on the Skin Site Assessments. Noticeable erythema (the mildest category, grade 1), $\leq$ 50% occluded area observed in 3 subjects (2 in DURAGESIC treatment group and 1 in D-TRANS treatment group) 1 hour after removal of the systems.

One ASR of each of the following was recorded, all from the DURAGESIC treatment group: papules with $\leq 50\%$ of the occluded area, and itching of mild severity. All but 1 (papules with $\leq 50\%$ of the occluded area) of the application site reactions were resolved within 24 hours after system removal.

STUDY LIMITATIONS: [No notable study limitations were identified by the Sponsor.

CONCLUSION: The 100 $\mu\text{g/hr}$ D-TRANS fentanyl matrix system was bioequivalent to the 100 $\mu\text{g/hr}$ DURAGESIC fentanyl reservoir system. The D-TRANS fentanyl matrix system and the DURAGESIC fentanyl reservoir system were considered safe and well tolerated when concomitantly administered with naltrexone in this healthy subject population.

Appendix 2. Reviewer's Analysis Results

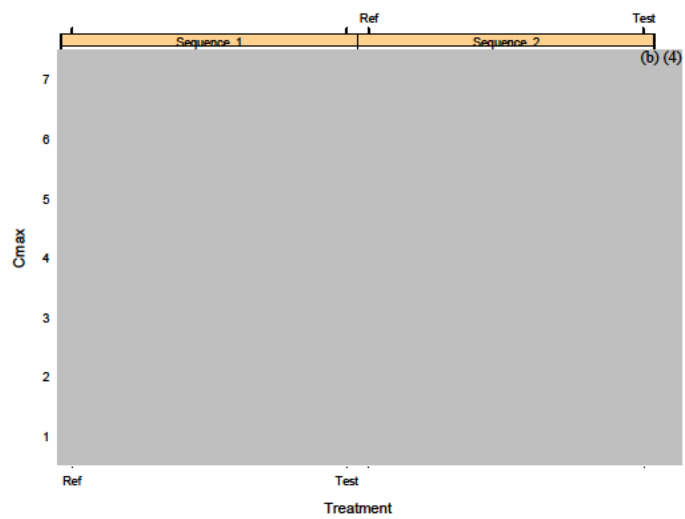
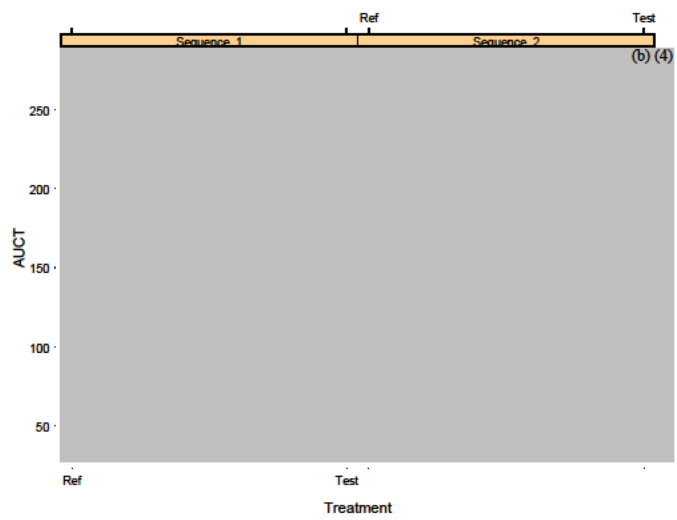
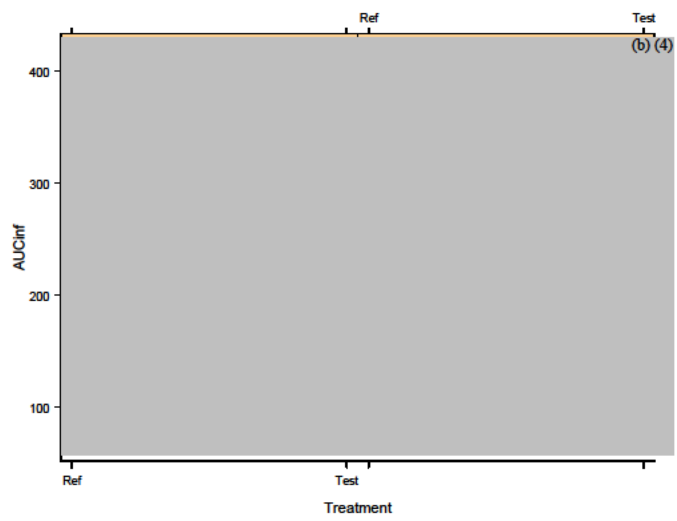
Study Design: The study is a 2 treatment, 2 period, 2 sequence crossover study in 91 subjects as shown in the following table.

Class	Levels
Subject	91
Sequence	2
Period	2
Treatmen	2

Results: The sample size, arithmetic mean, CV, median and range values for each parameter and their log transformed values are shown in the following table. In the table, AUCI, AUCt, Cmax, TMAX, LAMBDZ, T12, refer to AUC to infinite, AUC to last time point, Cmax, Tmax, LamdaZ, T-half, respectively; LAUCI, LAUCT, LCMAX, are log transformed AUCI, AUCt, Cmax, values, respectively. TestN and RefN are the sample sizes for the test product and reference product, respectively.

Parameter	Reference					Test				
	N	Mean	CV%	Median	Range	N	Mean	CV%	Median	Range
AUCI	81	155.28	33.72	150.30	217.72	79	166.61	38.19	164.69	339.64
AUCT	83	133.96	31.74	134.10	183.57	79	147.06	36.65	142.40	226.42
CMAx	83	2.29	35.90	2.15	4.39	79	2.39	45.00	2.10	6.47
LAMBDZ	81	0.03	28.56	0.03	0.04	79	0.03	28.54	0.03	0.04
LAUCI	81	4.99	6.98	5.01	1.47	79	5.05	7.28	5.10	1.78
LAUCT	83	4.84	7.34	4.90	1.80	79	4.92	7.50	4.96	1.65
LCMAx	83	0.76	48.33	0.77	1.76	79	0.78	52.97	0.74	2.19
T12	81	25.98	34.89	23.56	49.60	79	26.91	33.25	24.77	43.74
TMAx	83	43.44	33.65	42.00	60.00	79	40.24	48.28	42.00	70.00

The AUC to infinite, AUC to last time point, Cmax, for each subject are plotted against the treatment, respectively, as shown in the following figures.



The following table shows the geometric means of AUC to infinite, AUC to last time point, Cmax, TestGeoMean and RefGeoMean refer to the geometric means of each parameter for test product and reference product, respectively.

Parameter	TestN	RefN	TestGeoMean	RefGeoMean
AUCI	81	79	146.56	155.80
AUCT	83	79	126.56	137.68
CMAx	83	79	2.15	2.19

The fit statistics of the ANOVA analysis is summarized in the following table. The R-Square (RSquare) measures how much variation in the log transformed parameter can be accounted for by the model. The larger the value, the better the model's fit. The Coefficient of variation (CV) describes the amount of variation of the log transformed parameter in the population. DepMean is the mean of the parameter (log transformed). RootMSE estimates the standard deviation of the parameter (log transformed) and equals the square root of the Mean Square for Error.

Parameters	RSquare	CV	RootMSE	DepMean
LCMAx	0.899	23.856	0.184	0.773
LAUCT	0.939	2.737	0.134	4.882
LAUCI	0.928	2.842	0.143	5.018

The results of the comparison between the text product and the reference product are summarized in the following table. In the table, LowerCL, Difference and UpperCL refer to the differences (Test-Ref) of log transformed means and their lower and upper 90% confidence limits, respectively. Ratio, U_LCI, L_LCI are the ratios (Test/Ref) of the geometric means and their lower and upper 90% confidence limits, respectively.

Parameters	LowerCL	Difference	UpperCL	Ratio	U_LCI	L_LCI
LCMAx	0.006	0.056	0.107	105.813	111.263	100.629
LAUCT	0.064	0.101	0.137	110.614	114.713	106.662
LAUCI	0.054	0.093	0.132	109.711	114.083	105.507

Conclusions: The study results show that the test product is bioequivalent to the reference product. The 90% confidence intervals of the ratios of geometric means for AUC (0 to infinite), AUC (0-last time point) and Cmax all fall inside 80% to 125% limits.

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

/s/

John Duan
5/8/2009 09:46:39 AM
BIOPHARMACEUTICS

Patrick Marroum
5/8/2009 09:48:55 AM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: NDA 19-813/SCF-044

Name of Drug: Duragesic (fentanyl transdermal system)

Applicant: Johnson and Johnson

Material Reviewed:

Submission Date(s): January 30, 2009

Receipt Date(s): January 30, 2009

Submission Date of Structure Product Labeling (SPL): January 30, 2009

Type of Labeling Reviewed: WORD

Background and Summary

Supplemental application S-044 provides for a formulation change of Duragesic from a reservoir system to a matrix system. This is a CMC Prior Approval Supplement. The labeling changes reflect the change in formulation.

This label was compared to the last approved label, S-033, approved February 7, 2008.

Status Report

Reviews Completed: Kathleen Davies, PM, 7/16/09

Review Concurrence: Sara Stradley, Chief, Project Management Staff, 7/30/09
Ellen Fields, Clinical Team Leader, 7/30/09

RPM Review – PI

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label. Sections without changes were omitted.

BOX WARNING:

The following text was revised on the second page of the box warning (paragraph immediately below contraindication warning):

“Since the peak fentanyl concentrations generally levels occur between 20 24 and 72 hours of treatment, prescribers should...”

The Division ACCEPTS this revision.

At the bottom of page 2 of the boxed warning, the following edits were made by the Sponsor:

“Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose (see DOSAGE And ADMINISTRATION – Initial DURAGESIC® Dose Selection). Due to the mean ~~elimination~~ half-life of approximately 20-27 ~~17~~ hours of DURAGESIC, patients who are thought to have had...”

The Division ACCEPTS this revision. Clinical pharmacology concurred.

On page 3 of the boxed warning, second to last paragraph, the following edits were made:

“DURAGESIC patches are intended for transdermal use (on intact skin) only. Do not use DURAGESIC patch if the pouch seal is broken or then patch is cut, damaged, or changed in any way. ~~Using a patch that is cut, damaged, 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.~~”

The Division ACCEPTS this revision.

DESCRIPTION:

Under the System Components and Structure section, the following edits were made:

“The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/h per 10 cm²). The composition per unit area of all system sizes is identical. ~~Each system also contain 0.1 mL of alcohol USP per 10 cm².~~”

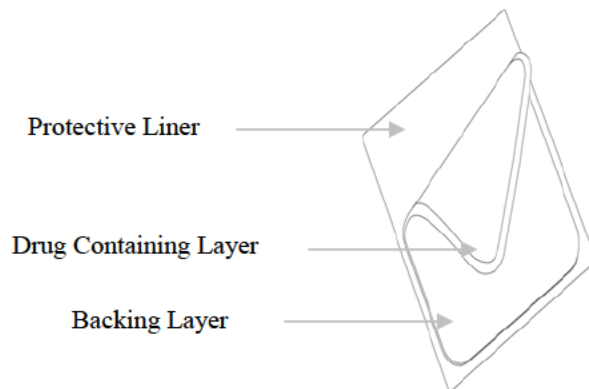
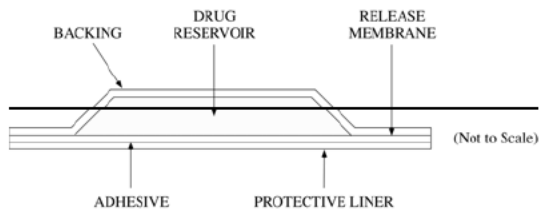
Dose* (mcg/h)	Size (cm ²)	Fentanyl Content (mg)
12**	55.25	1.25 <u>2.1</u>
25	10 <u>10.5</u>	2.5 <u>4.2</u>
50	20 <u>21</u>	5 <u>8.4</u>
75	30 <u>31.5</u>	7.5 <u>12.6</u>
100	40 <u>42</u>	10 <u>16.8</u>

*Nominal delivery rate per hour

**Nominal delivery rate is 12.5 mcg/hr

DURAGESIC[®] is a rectangular transparent 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/ethyl vinyl acetate film; 2) a drug-in-adhesive layer ~~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.



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.~~

The Division ACCEPTS these changes. Clinical team concurred.

CLINICAL PHARMACOLOGY:

The following changes were made under Pharmacology (2nd paragraph):

“Analgesic blood concentrations ~~levels~~ of fentanyl may cause nausea and vomiting...”

The Division ACCEPTS this change.

The following changes were made under Pharmacokinetics:
1st paragraph:

The DURAGESIC® (fentanyl transdermal system) releases fentanyl is a drug-in-adhesive matrix designed formulation. Fentanyl is released from the matrix reservoir at a nearly constant amount per unit time. The concentration gradient existing between the matrix saturated solution of drug in reservoir 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 matrix copolymer release membrane and the diffusion of fentanyl through the skin layers.

The Division ACCEPTS these revisions.

In the second paragraph, the last sentence was deleted:

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 50, 75, and 100 mcg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient. ~~The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate limiting copolymer membrane and increases the permeability of the skin to fentanyl.~~

The Division ACCEPTS these revisions.

In the third paragraph, the following edits were made:

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~~ 20 and 72 hours after initial application (see Table A). Serum fentanyl concentrations achieved are proportional to the DURAGESIC® delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first ~~few two~~ system applications. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size. ~~After several sequential 72-hour applications, patients~~ 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 100 mcg/hr DURAGESIC patch were bioequivalent with or without a Bioclusive overlay (polyurethane film dressing).

The Division ACCEPTS these revisions.

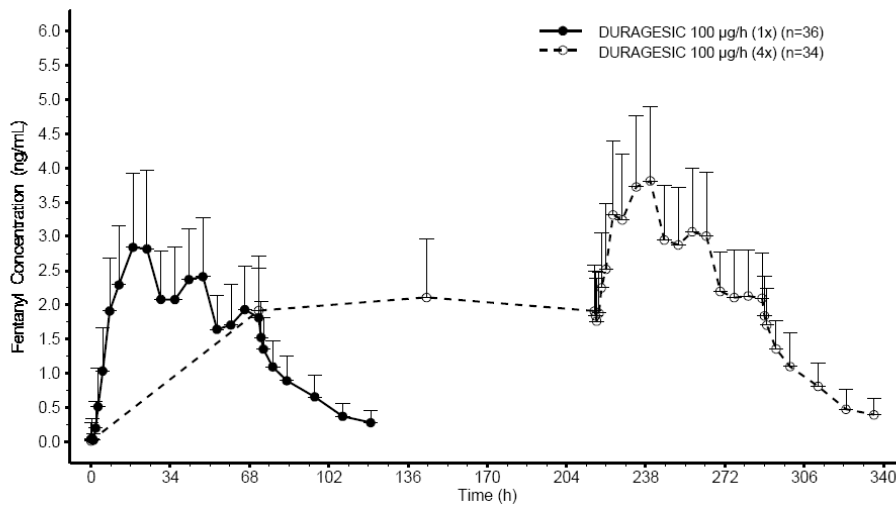
Fourth paragraph edits:

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13-22) 20-27 hours following a 24 hour application.

The Division ACCEPTS these changes. Clinical Pharmacology concurred.

The new Graph and table were revised to reflect the new formulation:

**Serum Fentanyl Concentrations
Following Single and Multiple Applications of DURAGESIC® 100 mcg/h (n=10)**



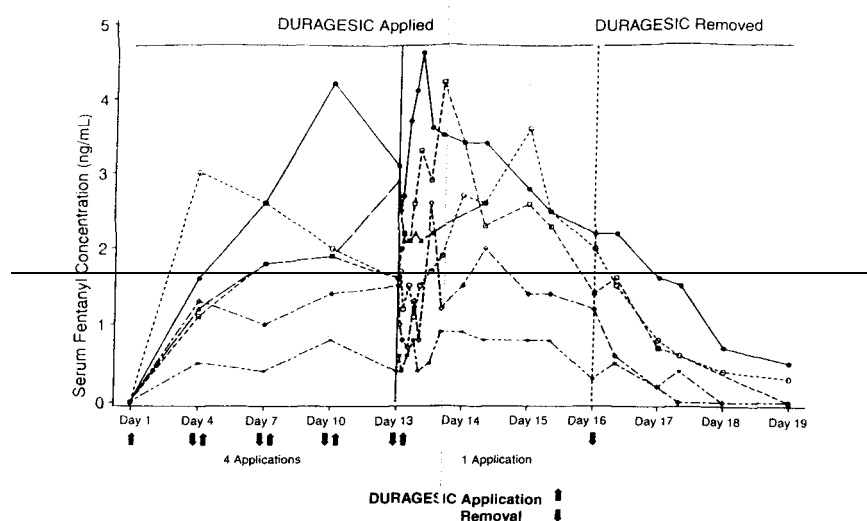


TABLE A: FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

	Mean (SD) Time to Maximal Concentration Tmax (h)	Mean (SD) Maximal Concentration Cmax (ng/mL)
DURAGESIC® 12 mcg/h	27.528.8 (9.613.7)	0.30.38 (0.20.13)*
DURAGESIC® 25 mcg/h	38.131.7 (18.016.5)	0.60.85 (0.30.26)
DURAGESIC® 50 mcg/h	34.832.8 (15.415.6)	1.41.72 (0.50.53)
DURAGESIC® 75 mcg/h	33.535.8 (14.514.1)	1.72.32 (0.70.86)
DURAGESIC® 100 mcg/h	36.829.9 (15.713.3)	2.53.36 (1.21.28)

*Cmax values dose normalized from 4 x 12.5 mcg/h

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in ~~47~~ approximately 20-27 hours.

Under **Geriatric Use**, the following edits were made:

~~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 DURAGESIC® (fentanyl transdermal system) is unknown at this time.~~ Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the DURAGESIC® fentanyl transdermal patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours.

The Division ACCEPTS this revision. Clinical Pharmacology concurred.

INDICATIONS AND USAGE

No changes noted

CONTRAINDICATIONS

No changes noted

WARNINGS

The following changes were noted in the 1st paragraph:

Do not use DURAGESIC[®] patch if the pouch seal is broken or the patch is cut, damaged or changed in any way. ~~Using a patch that is cut, damaged, 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.~~

The Division ACCEPTS this revision.

In the 3rd paragraph, the following edits were made:

The mean ~~elimination~~ half-life of DURAGESIC[®] is ~~17~~ approximately 20-27 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after DURAGESIC[®] removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations ~~17~~ 20-27 hours after system removal.

The Division ACCEPTS these changes. Clinical Pharmacology concurred.

In the 5th paragraph, the following text was added:

All patients and their caregivers...death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the DURAGESIC[®] system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

The Division ACCEPTS these changes. Clinical Pharmacology concurred.

Under **Hypoventilation**, the following edits were made to the 2nd paragraph:

Because significant amounts of fentanyl continue to be ~~are~~ absorbed from the skin for 20-27 ~~17~~ hours or more after the patch is removed, hypoventilation may persist...stabilized.

The Division ACCEPTS these changes. Clinical Pharmacology concurred.

DRUG ABUSE AND ADDICTION

The following edits were made to the last paragraph in this section:

DURAGESIC[®] patches are intended for transdermal use (to be applied on the skin) only. Do not use a DURAGESIC[®] patch if the pouch seal is broken or if the patch is cut, damaged, or changed in any way. ~~Using a patch that is cut, damaged, 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.~~

The Division ACCEPTS these changes.

PRECAUTIONS

The following edits were made:

Under **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~~ concentration of the drug, and/or administration of an antagonist.

The Division ACCEPTS these changes.

Under **Information for Patients**:

4. Patients should be advised that DURAGESIC[®] should be applied immediately upon removal from the sealed ~~package~~ pouch and after removal of the protective liner. Additionally the patient should be advised of the following:
 - The DURAGESIC[®] patch should not be used if the pouch seal is broken, or if the patch is cut, damaged, or changed in any way. ~~Using a patch that is cut, damaged, 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.
10. ~~Patients should be instructed that, if the gel from the drug reservoir 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.~~

The Division ACCEPTS these changes.

Under **Carcinogenesis, Mutagenesis, and Impairment of Fertility**:

~~Studies in animals to evaluate the carcinogenic potential of fentanyl HCl have not been~~

~~conducted. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females.~~ (b) (4)

The Division revised this text to the following:

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.1 and 0.4 times the human daily dose obtained via the 100 mcg/hr patch based on body surface area comparison) (b) (4)

The Sponsor proposed the following revisions on July 29, 2009:

(b) (4)

The Division disagreed with the incorporation of Cmax values and instead revised this text to read:

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females. (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on AUC_{0-24h} comparison) (b) (4)

The Sponsor ACCEPTED this revision.

Under 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 DURAGESIC® (fentanyl transdermal system) is unknown at this time.~~ Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the

DURAGESIC® fentanyl transdermal patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours.

The Division ACCEPTS these changes.

ADVERSE REACTIONS

No changes noted

OVERDOSAGE

The following edits were made to the last paragraph in this section:

DURAGESIC® patches are intended for transdermal use (to be applied on the skin) only. Do not use a DURAGESIC® patch if the pouch seal is broken or if the patch is cut, damaged, or changed in any way. ~~Using a patch that is cut, damaged, 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.~~

The Division ACCEPTS these changes.

DOSAGE AND ADMINISTRATION

The following changes were noted in the 2nd paragraph under **Special Precautions**:

DURAGESIC® patches are intended for transdermal use (on intact skin) only. The DURAGESIC® patch should not be used if the pouch seal is broken, or the patch is cut, damaged, or changed in any way. ~~Using a patch that is cut, damaged 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.~~

The Division ACCEPTS these changes.

In the 4th paragraph, the following edits were made:

Overestimating the DURAGESIC® 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 approximately 20-27 ~~17 hours of DURAGESIC®~~, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

The Division ACCEPTS these changes. Clinical pharmacology concurred.

In the second to last paragraph before **Dose Selection**, the following edits were made:

DURAGESIC[®] should be applied immediately upon removal from the sealed package. Do not use if the pouch seal is broken.

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.~~

The Division ACCEPTS these changes.

Under **Initial DURAGESIC Dose Selection**, the following edits were made:

Overestimating...first dose. Due to the mean ~~elimination~~ half-life of approximately 20-2717 hours of DURAGESIC[®], patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

The Division ACCEPTS these changes. Clinical pharmacology concurred.

HOW SUPPLIED

The following text was edited:

DURAGESIC[®] (fentanyl transdermal system) is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC [®] Dose (mcg/h)	System Size (cm ²)	Fentanyl Content (mg)	NDC Number
DURAGESIC [®] -12	<u>55.25</u>	<u>1.25</u> 2.1	50458-037 <u>090</u> -05
DURAGESIC [®] -25	<u>10</u> 10.5	<u>2.5</u> 4.2	50458-033 <u>091</u> -05
DURAGESIC [®] -50	<u>20</u> 21	<u>5</u> 8.4	50458-034 <u>092</u> -05
DURAGESIC [®] -75	<u>30</u> 31.5	<u>7.5</u> 12.6	50458-035 <u>093</u> -05
DURAGESIC [®] -100	<u>40</u> 42	<u>10</u> 16.8	50458-036 <u>094</u> -05

Safety and Handling

DURAGESIC[®] is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. ~~If the gel from the drug reservoir accidentally contacts the skin, the area 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. Do not use a DURAGESIC[®] patch if the seal is broken or the patch is cut, damaged, or changed in any way. Using a patch that is cut, damaged, 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.~~

KEEP DURAGESIC[®] OUT OF THE REACH OF CHILDREN AND PETS.

(b) (4)

The Division revised this text to:

Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). Apply immediately after removal from individually sealed pouch. Do not use if the pouch seal is broken. **For transdermal use only.**

The Sponsor ACCEPTS this change.

RPM Review – MG

In the medication guide, minor editorial changes were made to match the PI. These included adding the word “pouch” in front of seal under “How should I use DURAGESIC;” revising the storage and handling conditions under “How should I store DURAGESIC,” (b) (4) and revising the active ingredients list to comprise the components of the new matrix patch.

The Division DISAGREED with this edit and proposed the following storage statement:

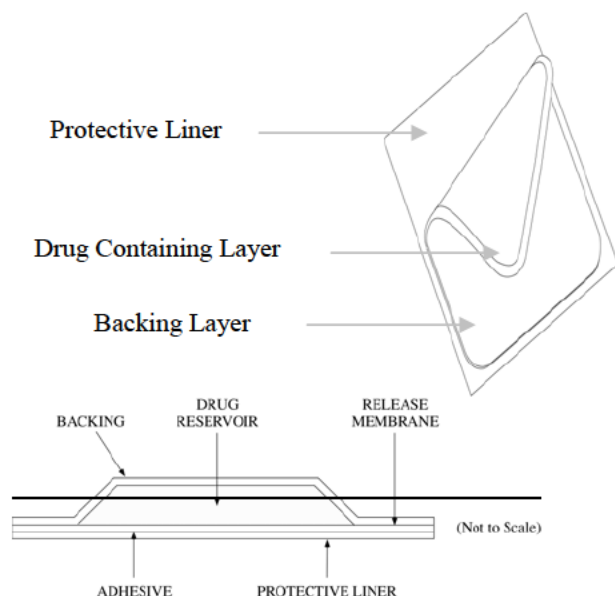
Store at room temperature.

The Sponsor ACCEPTS this change.

RPM Review – IFU

The following edits were made to the IFU:

Instructions for Applying a DURAGESIC[®] patch



Before Applying DURAGESIC®

- ~~DURAGESIC® is a patch with a medicine gel sealed inside. The patch is designed to keep the medicine gel from getting on your hands or body. If the gel from the patch 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 gel because they may increase the medicine's ability to go through the skin.~~
- Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged or changed in any way.

Applying a DURAGESIC® Patch

3. Open the Pouch: Fold and tear at slit or cut along the label edge taking care so as to not cut the patch. ~~Tear open the pouch along the dotted line, starting at the slit, and remove a~~ the DURAGESIC® patch. Each Duragesic® patch is sealed in its own protective pouch. Do not remove the Duragesic® patch from the pouch until you are ready to use it (see Figure 6).

4. Peel: Peel off both parts of the protective liner from the back of the patch and throw away. Each DURAGESIC® patch has a clear plastic backing that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this backing off. Throw the clear plastic backing away. Touch the sticky side of a the DURAGESIC® patch as little as possible (see Figure 7).

The Division ACCEPTS these changes.

Recommendations

Approve S-044.

Kathleen Davies, M.S.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sara Stradley, M.S.
Chief, Project Management Staff

Drafted: KMD/17July 2009

Revised/Initialed:

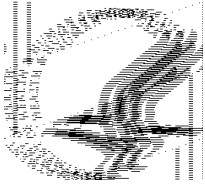
Finalized:

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

/s/

KATHLEEN M DAVIES
07/30/2009

ELLEN W FIELDS
07/30/2009
concur



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

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M E M O R A N D U M

Date: June 15, 2009

From: Snezana Trajkovic, MD, Medical Officer

Through: Susan Walker, MD, Division Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP

To: Bob Rappaport, MD, Division Director, DAARP
Elizabeth Kilgore, MD, Medical Officer, DAARP

CC: Barbara Gould, CPMS, DDDP
Nichelle E. Rashid, Regulatory Project Manager, DDDP
Kathleen Davies, RPM, DAARP

Re: DDDP Consult #1148

A CMC prior approval supplement for Duragesic (fentanyl transdermal product), NDA 19-813 was submitted to DAARP on May 21, 2009. This product has been changed to convert a reservoir patch to a matrix patch. DAARP requests DDDP to evaluate two studies in the CMC submission related to contact sensitization and photosensitivity. This product, D-TRANS, which they used in these studies, is the same as the proposed matrix Duragesic product proposed.

Conclusion:

The Division recommends that provocative studies to evaluate dermal safety should be performed to assess safety prior to marketing for topical drug products. These include cumulative irritation, sensitization, phototoxicity, and photoallergenicity evaluations.

The sponsor previously submitted two protocols for evaluation and DDDP was consulted to review the adequacy of the dermal safety assessments. Though specific concerns regarding the adequacy of these protocols were communicated to the sponsor in April, 2001, the studies appear to have been conducted without the suggested amendments.

The applicant has not conducted dermal safety evaluations that DDDP typically recommends for topical products, and the submitted studies would not be considered to be adequate provocative dermal safety evaluations of the patch product.

However, the Division recognizes the difficulty with performing 21 day sensitization/irritation studies with the active drug containing patch, particularly in products containing opioids. If the sponsor has conducted a systematic algorithm to assess and record irritation of active fentanyl containing patches in actual use conditions during the phase 3 trials, and has sufficient international post marketing experience, then the primary review division may reasonably conclude that they have an adequate safety database (b) (4). In this situation, the need for specific provocative dermal safety studies could be waived by the primary review division.

The results of trial C-2002-050-01 are not adequate to conclude that significant Contact Sensitization did or did not occur, since the open label nature of the study could incorporate observer bias.

Phototoxicity did not occur during conduct of dermal safety studies with the product, but this finding is (b) (4) (Trial C-202-053-02).

However, during the conduct of trial C-2002-050-01 an irritancy signal was noted.

Therefore, if the phase 3 trial data in combination with the post marketing safety experience is deemed adequate for labeling, additional studies for topical safety may not be necessary. If the safety database is deemed not adequate, then a Cumulative Irritancy/Sensitization trial is recommended to support the dermal safety of the sponsor's product. Additionally, DDDP recommends that Photoallergenicity study be conducted in order to complete dermal safety evaluation of the product.

Background

Duragesic is drug product that contains fentanyl, a synthetic opioid with potent analgesic properties. Fentanyl is available in several dosage forms and administration devices, including two transdermal formulations, DURAGESIC and D-TRANS.

DURAGESIC fentanyl is a reservoir formulation utilizing a form-fill-seal design that contains fentanyl and alcohol gelled in a drug reservoir. DURAGESIC is approved drug product developed under NDA 19813 and was approved on August 7, 1990.

D-TRANS fentanyl is a matrix formulation in which fentanyl base is incorporated directly into a single layer of pressure-sensitive acrylate adhesive. D-TRANS is marketed in the European Union and worldwide, and is not available in US. The dose strength for D-TRANS is the same as those for DURAGESIC: 12.5; 25; 50; 75 and 100µg/h all of which are currently marketed worldwide.

The sponsor submitted CMC Supplemental New Drug Application (s NDA) under NDA 19813 for the D-TRANS system (Matrix Patch), S-044 on January 30, 2009. In the CMC supplement the sponsor submitted 9 Phase I trials which included two dermal safety trials: C-2002-050 (Contact sensitization) and C-2002-053 (Phototoxicity).

The protocols for the two submitted completed studies were evaluated in a previous consult by Dr. Ramzy S. Labib of DDDP on February 6, 2001. Pertinent recommendations at that time included:

Protocol C-2000-019-00

1. An open label study cannot be considered adequate. The testing of two other products, preferably a positive (e.g. sodium lauryl sulfate) and a negative control (e.g. Baby shampoo), and randomization, may help in the design of a double-blind protocol. These controls are positive and negative regarding irritation rather than contact sensitization. Therefore, no cross sensitization is expected from their use.
2. The testing of D-TRANS placebo rather than the active formulation may be acceptable, assuming that Duragesic has been adequately tested for its contact sensitizing potential.
3. The number of evaluable subjects in this study should not be less than 200 in order to give any meaningful results, taking into consideration that contact sensitization is not a common event. Therefore, a larger number of subjects should be enrolled to assure 200 evaluable subjects at the end of the study.
4. In the case of positive sensitization in the challenge phase, it is advisable to test the individual ingredients to identify the sensitizing agent.

Protocol C-2000-020-00:

1. If there is no appreciable UVA or UVB absorption by the active ingredient or the final product, then there is no need for this study.
2. If the active ingredient has appreciable UVA or UVB absorption, we recommend that you test at least the 25 µg/hr product.

These comments were communicated to the sponsor by facsimile on April 26, 2001. The study reports do not reflect any changes recommended in this previous consult as noted below in the review of the individual studies.

Materials Evaluated:

Trial C-202-053-02

Trial C-2002-050-01

Review:

The following trials were submitted in support of the current application for D-TRANS fentanyl matrix system.

Trial C-2002-053-02

Principal Investigator: Norma Kellett MBChB, MRCGGP, FFPM

Trial Title: Evaluation of the Phototoxicity of D-TRANS Fentanyl Matrix System in Healthy Subjects (Protocol C-2002-053-02)

Trial Population: 38 healthy male and female subjects 18 to 45 years of age were enrolled and 30 subjects completed the trial.

Trial Design and Procedures:

This was a single-center, randomized, double-blind study to evaluate phototoxic potential of D-TRANS fentanyl matrix system in healthy adult subjects.

On Day 1, two D-TRANS fentanyl systems 1 cm² (2.4 µg/h), and two D-TRANS placebo systems 1 cm² were applied to skin sites on the subjects backs. On Day 2, all four D-TRANS systems were removed approximately 24 hours (+/- 15 minutes) after the systems had been applied, and the skin sites were assessed for topical adverse events. Within 15 minutes of system removal, on the left side of each subject's back, two application sites (one with a D-TRANS fentanyl system and one with a D-TRANS placebo system) and an un-patched skin site were exposed to 15 joules/cm² of ultraviolet (UVA) light. Two application sites on the right side of each subject's back were not irradiated. Subjects were monitored for topical reactions (erythema, edema, papules, pustules, and itching) immediately after system removal and immediately after irradiation. Additionally, skin assessments were made approximately 24 and 48 hours after irradiation.

Adhesion of each D-TRANS system applied was assessed at the time of system removal.

Inclusion Criteria:

1. Male or female subjects between 18 and 45 years of age.
2. Subjects who were healthy volunteers with no clinically relevant abnormalities as determined by medical history, physical examination, blood chemistry, complete blood count (CBC), urinalysis, and electrocardiogram (ECG).
3. Subjects who refrained from using corticosteroids (systemic or topical) and immune modifiers throughout the study period.
4. Subjects who consented to use a medically acceptable method of contraception throughout the entire study period and for 1 week after the study was completed. Medically acceptable methods of contraception that could be used by the subject and/or the subject's partner included abstinence, birth control pills or patches, diaphragm and spermicide, intrauterine contraceptive device, condom and vaginal spermicide, surgical sterilization, vasectomy, or progestin implant or injection. Women who were post-menopausal also met this inclusion criterion.
5. Female subjects of childbearing potential who had a negative urine pregnancy test at screening and upon admission to the study site.
6. Subjects who had a negative urine drug test at study screening and upon admission to the study site. Urine was tested for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opioids.
7. Subjects who had a negative alcohol analysis upon admission to the study site.
8. Subjects who refrained from taking a bath, showering, and swimming while wearing the system.
9. Subjects who provided written consent to participate in the study and who understood that they were free to withdraw from the study at any time.
10. Subjects who were able to understand the study procedures and were willing to follow them.

5.4.3 Exclusion Criteria:

1. Subjects with clinically significant medical conditions (dermatologic, psychiatric, respiratory, cardiovascular, hepatic, renal, gastrointestinal, hematologic, genito-urinary, and gynecologic) or other organ abnormality or pathology.
2. Subjects with a history of chronic obstructive pulmonary disease or any lung disease (eg, asthma) that would cause CO₂ retention.
3. Subjects with active or chronic (in remission) systemic skin disease, or with active local skin disease that would preclude application of the study system.
4. Subjects with skin pigmentation (back tattoos) that would interfere with the ability to assess irritation at the application site.
5. Subjects with recent extensive exposure to natural or artificial light on their backs.
6. Subjects who planned to use sunscreen or tanning lotions 1 week before the study started and during the study.
7. Subjects who had a known allergy or hypersensitivity to fentanyl or other opioids, or to skin adhesives.
8. Females who were pregnant or breast-feeding.

9. Subjects who had used systemic or topical analgesics or antihistamines within 72 hours before the study started, or who had used systemic or topical corticosteroids within 1 week before the study started.
10. Subjects who used any known phototoxic drugs (doxycycline, tetracycline, quinolones, sulfonamides, feldene, Retin-A).
11. Subjects who had used monoamine oxidase inhibitors (MAOIs) within 21 days before study Day 1.
12. Subjects who planned to use topical analgesics or antihistamines, systemic or topical corticosteroids, known phototoxic drugs, or monoamine oxidase inhibitors (MAOIs) during the study.
13. Subjects who had taken an investigational drug within the last 30 days before the first system application or within a period of less than five times the drug's half-life, whichever was longer.
14. Subjects with a history or presence of drug or alcohol dependence or abuse as defined in protocol.
15. Subjects who, in the investigator's opinion, might not be capable of following the study schedule for any reason.

The topical reactions were scored using the following scales:

Severity of Erythema

- 0 = None
- 1 = Noticeable redness
- 2 = Well-defined redness
- 3 = Beet redness

Extent of Erythema

- 0 = None
- 1 = <50% occluded area
- 2 = >50% occluded area

Extent of Papules

- 0 = None
- 1 = <50% occluded area
- 2 = >50% occluded area

Extent of Pustules

- 0 = None
- 1 = <50% occluded area
- 2 = >50% occluded area

Extent of Edema

- 0 = None
- 1 = <50% occluded area
- 2 = >50% occluded area

Severity of Itching

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

To confirm phototoxicity events, a dermatologist was to examine the skin site within 24 hours if any of the following reactions were noted by the medical staff:

- Score of 2 or above on the Severity of Erythema Scale
- Score of 2 for Extent of Papules and/or Extent of Edema
- Score of 1 or above for Extent of Pustules

Color photographs were to be taken to document the development of possible phototoxicity responses.

Using the following scale, the adherence of each D-TRANS system was assessed before the system was removed:

Adherence of System:

- 0 = system adhered to at least 90% of the area and no edges unattached
- 1 = system between 75 and 89% adhered
- 2 = system between 50 and 74% adhered
- 3 = system less than or equal to 49% adhered
- 4 = system no longer adhered to skin

Safety monitoring: Physical examination, vital signs, urine drug test, alcohol breath test, urine pregnancy test (for women of child-bearing potential), laboratory tests (blood chemistry, CBC, urinalysis) and ECG were performed at screening. Application site assessments were made during the trial and at trial termination. At trial termination (or early termination), a physical exam, an electrocardiogram, and clinical laboratory tests were performed; vital signs were measured; and application sites were assessed. Ongoing adverse events and concomitant medications were followed until the adverse events resolved or became medically stable.

Trial results:

Table 1: Number (%) of Subjects with Erythema after System Removal and After Irradiation

Time point	Erythema Score	D-TRANS fentanyl irradiated	D-TRANS fentanyl Non-irradiated	D-TRANS placebo irradiated	D-TRANS placebo Non-irradiated	Un-patched Skin site irradiated
Immediately after system removal	0	4 (10.8)	5 (13.2)	10 (27.0)	11 (28.9)	37 (100)
	1	33 (89.2)	32 (84.2)	27 (73.0)	26 (68.4)	0
	2	0	1 (2.6)	0	1 (2.6)	0
	3	0	0	0	0	0
Immediately after irradiation	0	3 (8.1)	1 (2.6)	8 (21.6)	12 (31.6)	31 (83.8)
	1	34 (91.9)	36 (94.7)	29 (78.4)	25 (65.8)	6 (16.2)
	2	0	0	0	0	0
	3	0	0	0	0	0
24 hours after irradiation	0	5 (13.5)	33 (86.8)	5 (13.5)	34 (89.5)	14 (37.8)
	1	32 (86.5)	5 (13.2)	32 (86.5)	4 (10.5)	23 (62.2)
	2	0	0	0	0	0
	3	0	0	0	0	0
48 hours after irradiation	0	13 (35.1)	38 (100)	13 (35.1)	38 (100)	18 (48.6)
	1	24 (64.9)	0	24 (64.9)	0	19 (51.4)
	2	0	0	0	0	0
	3	0	0	0	0	0

Source: sponsor's submission

Table 2:
Topical Adverse Events

Timepoint	Score	Erythema Severity	Erythema Extent	Edema Extent	Papules Extent	Pustules Extent	Itching Severity
Immediately post removal (n=37)	0	4 (10.8%)	4 (10.8%)	37 (100%)	37 (100%)	37 (100%)	35 (94.6%)
	1	33 (89.2%)	8 (21.6%)	0	0	0	2 (5.4%)
	2	0	25 (67.6%)	0	0	0	0
	3	0					0
Immediately post- irradiation (n=37)	0	3 (8.1%)	3 (8.1%)	37 (100%)	37 (100%)	37 (100%)	35 (94.6%)
	1	34 (91.9%)	10 (27.0%)	0	0	0	2 (5.4%)
	2	0	24 (64.9%)	0	0	0	0
	3	0					0

Source: sponsor's submission

Immediately after system removal, the two fentanyl sites had a similar incidence of Erythema score of 1 or 2 (89.2% and 86.8%), and they had a higher incidence of erythema than the placebo sites (73.0% and 71.0%). The un-patched skin sites had no erythema.

Immediately after irradiation, the irradiated fentanyl sites had a similar incidence of erythema to the non-irradiated fentanyl sites (91.9% and 94.7% respectively). The placebo sites showed less erythema than fentanyl sites (78.4% for placebo irradiated and 65.8% for placebo non-irradiated).

There was a reduction in the incidence of erythema from the 24-hour assessment to the 48-hour assessment. At the 48 hour assessment, there was an identical incidence of erythema (64.9%) in the irradiated fentanyl and irradiated placebo sites, as well as a high incidence (51.4%) of erythema at the irradiated un-patched sites.

For the non-irradiated fentanyl and placebo sites, the majority of subjects (86.8% and 89.5%, respectively) had no erythema at the 24-hour assessment. None of the subjects (100%) had erythema at the 48-hour assessment.

Subject 111 had erythema and edema of different degrees at all four system sites immediately after system removal. Because of these topical reactions, the consulting dermatologist decided to refrain from further testing for this subject and this subjects has not been irradiated. Forty-six minutes after system removal, the topical reactions were assessed as almost certainly urticaria. This subject was evaluated thereafter. She was symptom free at the 24-hour assessment with one exception: erythema at one of the placebo sites.

Sponsor concluded that none of the topical reactions suggested a phototoxic reaction in any of the UV-exposed skin sites at any assessment times.

Safety:

Subject disposition: 37 subjects were randomized and 37 subjects completed the trial. No deaths or serious adverse events and no phototoxic reactions were reported in this trial. There were no discontinuations of subjects due to adverse events.

Following adverse events were reported:

Local adverse events:

Thirty-seven subjects were exposed to UV light. One subject, Subject 111, was not exposed to UV light. The most common topical adverse reaction at all four assessments was erythema (Table 1). In the majority of subjects, erythema was of noticeable redness (Score 1, the mildest category), and no subject had beet redness (Score 3) at any assessment.

Systemic adverse events:

All adverse events reported were of mild or moderate severity. The majority of subjects did not report any AEs (29 subjects, 76.3%). The most common adverse events classified as possibly related to treatment were headache (13.2%), nausea (10.5%), and vomiting (10.5%). One subject had elevated ALT, AST and GGT that was considered related to treatment. Elevated ALT and AST resolved within 16 days. The elevated GGT showed continuous decline towards normal within 16 days. Same subject had elevated GGT prior to entrance into the trial.

Vital Signs, Physical Findings, and Other Observations Related to Safety:

Vital signs (mean systolic and diastolic blood pressure, respiratory rate, pulse, and temperature) were similar at all four assessments. There were no identifiable trends at any time point.

ECG findings at termination showed no changes from screening values for any subject.

Table 3:**Adverse Events**

	Total (n=38)
Number of patients with no adverse event	29 (76.3%)
at least one adverse event	9 (23.7%)
Number of patients who reported adverse events by body system	
Body as a Whole	6 (15.8%)
Headache	5 (13.2%)
Extremity pain	1 (2.6%)
Digestive System	5 (13.2%)
Nausea	4 (10.5%)
Vomiting	4 (10.5%)
Metabolic and Nutritional System	1 (2.6%)
Gamma glutamyl transpeptidase increased	1 (2.6%)
SGOT increased	1 (2.6%)
SGPT increased	1 (2.6%)
Skin System	1 (2.6%)
Rash	1 (2.6%)
Urogenital System	1 (2.6%)
Hematuria	1 (2.6%)

Source: sponsor's submission

System Adhesion Evaluation

Adhesion of each D-TRANS system applied was assessed at the time of system removal. As shown in Table 4, all systems but one was adhered to at least 90% of the application area with no edges unattached for most subjects during the 24-hour wearing period.

Table 4:

	Treatment		
	D-TRANS Fentanyl (n=38)	D-Trans Placebo (n=38)	Total (n=38)
Number of systems applied	76 (100%)	76 (100%)	152 (100%)
System Adhesion Score			
0	75 (98.7%)	76 (100%)	151 (99.3%)
1	1	0	1(0.7%)
2	0	0	0
3	0	0	0
4	0	0	0

Reviewer's comment: The results of this trial C-2002-053-02 are adequate to conclude that phototoxicity did not occur during conduct of dermal safety with the product. However, the dose of the active drug was significantly lower than used in final product, and lower than the 25 µg/hr dose previously recommended by DDDP in the February, 2001 consult. Therefore, this study is not adequate to assess the true phototoxicity potential of D-TRANS fentanyl matrix system and the absence of phototoxicity from the current study (b) (4) if an approval action is taken by DAARP.

Adverse events reported were related to systemic effects of the drug product (fentanyl) and not due to patch product. Complete review of the safety during actual use in phase 3 trials and other submitted studies may be additionally relevant in determining the safety of the product.

Trial C-2002-050-01

Principal Investigator: Lisa V. Long, BS

Trial Title: Evaluation of the Contact Sensitization Potential of the Components of D-TRANS Fentanyl Matrix System, Exclusive of the Drug, in Healthy Subjects

Trial Population: 229 healthy male and female subjects 18 to 65 years of age were enrolled and evaluable data were available for 201 subjects.

Trial Design and Procedures: This was a single-center, open-label study in healthy volunteers to evaluate contact sensitization potential of the components of D-TRANS Fentanyl Matrix System, 42 cm², without the drug.

Induction Phase: subjects received 9 consecutive applications of a D-TRANS placebo matrix system to the same skin site on the upper outer arm. A different skin site on the same arm was

selected only if an intolerable skin reaction occurred at this application site. A change in application site was based on a skin reaction with a score of at least 2 on any of the application-site reaction scales (except for extent of erythema) or on the judgment of the consulting dermatologist. The first and second systems of each week were worn for 2 days (48 ± 4 hours) each and the third system for 3 days (72 ± 4 hours). Subjects who wore at least 8 systems during the Induction Phase were allowed to continue in the study.

Rest Phase: During the 2-week Rest Phase, subjects had no systems applied.

Challenge Phase: During the Challenge Phase, each subject had 1 system applied for 48 hours to a naive skin site on the upper outer area of the arm not used in the Induction Phase, if possible. Based on the results of the Challenge Phase, a re-challenge could be performed by applying 1 system for 48 hours to a naive skin site on the arm used in the Challenge Phase or, if necessary, the upper chest.

In the Challenge Phase, and, if applicable, the Re-challenge Phase, application sites were monitored for the development of a sensitization response at 1 h, 24 h, 48 h, and 72 h after system removal. A sensitization response was defined as a skin surface characterized by erythema, edema/induration, and plaques with or without vesicles of moderate or greater severity, all of which persisted for more than 24 hours after system removal. Application sites were monitored for possible occurrence of erythema, edema, papules, pustules, or itching at scheduled assessment times immediately after removal of each system and at 24 hours after removal of the last system. During the Challenge Phase, assessments of topical AEs at the application site were scheduled for 1 h, 24 h, 48 h, and 72 h after system removal. Other types of skin reactions observed at scheduled assessment times and all skin reaction observed at other times were reported as application-site reactions.

Re-challenge Phase: Subjects who exhibited a definite or possible skin sensitization reaction at the 72-hour assessment after removal of the challenge system were to be further evaluated by a re-challenge test. Prior to application of the re-challenge system, continued eligibility was to be confirmed as before. One system was to be applied to a naive skin site on the upper outer area of the arm used in the Challenge Phase (or, if necessary, on the upper chest) and worn for 48 hours. Topical AEs and sensitization reactions at the application site were to be assessed at 1 hour, 24 hours, 48 hours, and 72 hours after system removal.

Adherence of Systems:

The adherence of each induction system was assessed just before removal using the 6 point scale.

Inclusion Criteria:

1. Subjects had to be healthy males or females, as evidenced by review of the health questionnaire, between 18 and 65 years of age.
2. Subjects had to consent to use a medically acceptable method of contraception throughout the entire study period and for 1 week after the study had been completed. Medically acceptable methods of contraception that could be used by the subject were

abstinence, birth control pills or patches, diaphragm and spermicide, IUD, condom and vaginal spermicide, surgical sterilization, postmenopausal, vasectomy, or progestin implant or injection.

3. Female subjects of childbearing potential had to have a negative urine pregnancy test at screening.
4. Subjects were not allowed to engage in strenuous physical activity and had to be willing to keep the patches dry. They had to refrain from taking tub or hot tub baths, saunas, steam baths, swimming, and prolonged showers while wearing a system during the study.
5. Subjects had to agree not to use sunscreen or self-tanning lotions on the system application sites (bilateral upper arm and chest area).
6. Subjects had to provide written consent to participate in the study and understand that they were free to withdraw from the study at any time.
7. Subjects had to be able to understand and be willing to follow the study procedures.

Exclusion Criteria:

1. Subjects who had clinically significant medical problems (dermatologic, psychiatric, respiratory, cardiovascular, hepatic, renal, gastrointestinal, hematological, genitourinary, gynecologic) or other organ abnormality or pathology.
2. Subjects with active or chronic skin disease that precluded the application of the transdermal system or with chronic skin disease with risk of possible local exacerbation (psoriasis).
3. Subjects with skin pigmentation that would have interfered with the ability to score irritation (tattoos).
4. Subjects with a history of significant contact dermatitis (except for poison ivy/poison oak, nickel sensitivity, or perfume sensitivity).
5. Subjects who had a known allergy or hypersensitivity to any components of the test system (as listed in Section 5.5.2)
6. Subjects taking systemic or topical analgesics or antihistamines within 3 days prior to Day 1 and through the study, or systemic or topical corticosteroids within 21 days prior to Day 1 and through the study.
7. Subjects taking aspirin or nonsteroidal anti-inflammatory drugs within 14 days prior to Day 1 and throughout the study.
8. Subjects taking immune modifiers, or any other medications that in the opinion of investigator might affect test results.
9. Females who were pregnant (as demonstrated by a urine pregnancy test at screening) or breastfeeding.
10. Subjects who had taken an investigational drug within the past 30 days, or within a period of less than 5 times the drug's half-life, whichever was longer.
11. Subjects with a history or presence of alcohol or drug abuse (eg greater than 2 alcoholic drinks every day; 1 drink was defined as a half pint of beer, 1 measure of spirits, or 1 glass of wine).
12. Subjects who, in the investigator's opinion, might not be capable of following the study schedule for any reason.

The topical reactions were scored using the following scales:

Severity of Erythema

0 = None
1 = Noticeable redness
2 = Well-defined redness
3 = Beet redness

Extent of Erythema

0 = None
1 = <50% occluded area
2 = >50% occluded area

Extent of Papules

0 = None
1 = <50% occluded area
2 = >50% occluded area

Extent of Pustules

0 = None
1 = <50% occluded area
2 = >50% occluded area

Extent of Edema

0 = None
1 = <50% occluded area
2 = >50% occluded area

Severity of Itching

0 = None
1 = Mild
2 = Moderate
3 = Severe

Using the following scale, the adherence of each D-TRANS system was assessed

System Adhesion

0 = System adhered to at least 90% of the area
and no edges unattached
1 = System 75% to 89% adhered
2 = System 50% to 74% adhered
3 = System $\leq$ 49% adhered
4 = System no longer adhered to skin
5 = System taped

Safety monitoring:

For all female subjects of childbearing potential, a urine pregnancy test was performed at the time of study screening. Test results had to be negative to allow participation of the subject in the study. No vital signs were monitored in this study, since no active drug was administered.

Trial results:

A total of 229 subjects were enrolled in the study and had at least 1 D-TRANS placebo matrix system applied. Of these, 211 subjects received at least 8 transdermal systems during the Induction Phase. Of these 211 subjects, 203 entered the Challenge Phase and received a challenge system. 201 of those subjects were assessed for sensitization at 72 hours after removal of the challenge system and were considered evaluable. Three subjects discontinued early due to adverse events.

Table 5: Severity and Extent of Erythema during Challenge Phase

Time Post System Removal (n=189)				
	1 Hour	24 Hours	48 Hours	72 Hours
Erythema Severity				
Number of Subjects Assessed	188 (100%)	188 (100%)	188 (100%)	187 (100%)
None	166 (88.3%)	180 (95.7%)	185 (98.4%)	187 (100%)
Noticeable Redness	14 (7.4%)	7 (3.7%)	3 (1.6%)	0
Well Defined Redness	8 (4.3%)	1 (0.5%)	0	0
Beet redness	0	0	0	0
Missing Assessments	1	1	1	2
Erythema Extent				
Number of Subjects Assessed	187 (100%)	188 (100%)	188 (100%)	187 (100%)
None	166 (88.8%)	180 (95.7%)	185 (98.4%)	187 (100%)
<= 50% of occluded area	13 (7.0%)	7 (3.7%)	3 (1.6%)	0
> 50% of occluded area	8 (4.3%)	1 (0.5%)	0	0
Missing Assessments	2	1	1	2

Source: Sponsor's submission

Table 6: Extent of Edema during Challenge Phase

Time Post System Removal (n=189)				
	1 Hour	24 Hours	48 Hours	72 Hours
Edema Extent				
Number of Subjects Assessed	188 (100%)	188 (100%)	188 (100%)	187 (100%)
None	185 (98.4%)	188 (100%)	188 (100%)	187 (100%)
<= 50% of occluded area	1 (0.5%)	0	0	0
> 50% of occluded area	2 (1.1%)	0	0	0
Missing Assessments	1	1	1	2

Source: sponsor's submission

Table 7: Extent of Papules during Challenge Phase

Time Post System Removal (n=189)				
	1 Hour	24 Hours	48 Hours	72 Hours
Papules Extent				
Number of Subjects Assessed	188 (100%)	188 (100%)	188 (100%)	187 (100%)
None	167 (88.8%)	178 (94.7%)	185 (98.4%)	186 (99.5%)
<= 50% of occluded area	16 (8.5%)	10 (5.3%)	3 (1.6%)	1 (0.5%)
> 50% of occluded area	5 (2.7%)	0	0	0
Missing Assessments	1	1	1	2

Source: sponsor's submission

Table 8: Extent of Pustules during Challenge Phase

Time Post System Removal (n=189)				
	1 Hour	24 Hours	48 Hours	72 Hours
Pustules Extent				
Number of Subjects Assessed	188 (100%)	188 (100%)	188 (100%)	187 (100%)
None	187 (99.5%)	188 (100%)	188 (100%)	187 (100%)
<= 50% of occluded area	1 (0.5%)	0	0	0
> 50% of occluded area	0	0	0	0
Missing Assessments	1	1	1	2

Source: sponsor's submission

Table 9: Skin Sensitization Ratings during Challenge Phase

Time Post System Removal (n=203)				
	1 Hour	24 Hours	48 Hours	72 Hours
Sensitization Rating				
Number of Subjects Assessed	202(100%)	202(100%)	202 (100%)	201(100%)
Absent	178 (88.1%)	189 (93.6%)	194 (96.0%)	201 (100%)
Questionable	24 (11.9%)	13 (6.4%)	8 (4.0%)	0 Present
	0	0	0	0
Missing Assessments	1	1	1	2

Source: sponsor's submission

During the Induction Phase most noted local application site reaction were erythema and itching, which occurred in 5.8% and 4.9%, respectively, of assessed subjects after removal of the first system. All of the topical reactions seen after the first system removal were mild. With repeated applications of D-TRANS placebo matrix systems to the same skin site, incidence of topical reactions increased. After the removal of last system, erythema was reported in 54.3%, papules in 46.2%, itching in 7.7% and pustules in 1% of subjects. This increase in topical reactions were considered to be due skin irritation, not due to sensitization.

In the Induction Phase, 154 subjects (67.2%) required at least 1 application-site change due to skin reactions at the initial application site. The median time period before the first change in system application site was 13.9 days.

After the Challenge Phase, of the 201 evaluable subjects at 24-hour assessment timepoint, erythema was noted in 10.9% of subjects, papules were noted in 10.4% and itching in 9.4% of subjects. None of the reported erythema and itching was severe. Edema and pustules were seen in less than 2% of assessed subjects and only at 1 hour after system removal.

At 72 hour assessment timepoint, the only topical reactions noted were mild papules (resolved 2 days later) in 1 subject (1139), and no evaluable subject showed any topical reaction indicative of a skin sensitization reaction. All topical reactions seen during the Challenge Phase were judged as probably related to treatment.

The sponsor concluded that no contact sensitization has occurred during the conduct of this trial.

Safety:

During the Induction Phase, AEs were reported by 29 (12.7%) of the 229 treated subjects. Only one of these AEs was severe (tooth infection in Subject #1202), and only one AE was considered possibly related to study treatment (mild tingling of right arm in Subject #1177). AEs that occurred in more than 2 subjects during the Induction Phase were headache (2.2% of treated subjects), rhinitis (3.5%), cough (1.7%), respiratory disorder (1.7%), and pharyngitis (1.3%); none was considered treatment related. One subject (1068) discontinued the study early due rash, which was caused by poison ivy and judged as not related to study treatment. Most of AE were mild or moderate in severity.

Three subjects discontinued the study due to AEs:

- Subject 1068 discontinued due to a rash, which was caused by poison ivy and considered not related to study treatment.
- Subject 1142 discontinued after removal of the 4th induction system because of moderate itching judged as probably related to study treatment. This subject also showed well-defined redness and papules over more than 50% and edema over no more than 50% of the area occluded by the D-TRANS placebo matrix system.
- Subject 1201 discontinued after experiencing mild itching, judged as probably related to study treatment, after removal of the 2nd induction system. At the time of discontinuation, itching was continuing and medically stable. No follow up was provided.

During the Rest Phase, 1 case of severe accidental injury occurred (strained back muscle in Subject 1187), which was considered not related to study treatment.

All application site reaction reported during the Induction Phase (burning and stinging) were considered as probably treatment related, while the application site reactions reported during the Challenge Phase (scratch) was considered not treatment related. All treatment related AEs were AEs associated with transdermal applications and were of mild or moderate severity.

During the Challenge Phase, 3 of the 203 treated subjects reported AEs: tooth ache, back pain, and stiff neck, all of moderate severity and not related to study treatment.

No serious AEs were reported. 2 AEs were severe (tooth infection and strained back muscle) and considered not related to the study treatment. All other reported AE were of mild or moderate severity.

Reviewer's comment: *After reviewing the results of the trial C-2002-050-0, the following concerns are suggested:*

1. *This Open label trial design is not adequate to evaluate contact sensitization potential of the D-TRANS matrix system.*
2. *Additionally, it is noted that erythema and papules were reported in significant number of subjects after the induction phase of the trial (54.3% and 46.2% respectively).*

Although this trial was not designed to evaluate irritation potential of the D-TRANS placebo matrix system it has revealed an irritancy signal. DDDP recommends that the sponsor submits Cumulative Irritancy trial in support of the dermal safety of their product. If the product is to be labeled as an irritant, cumulative irritancy testing may not be needed.

The applicant has not conducted dermal safety evaluations that DDDP typically recommends for topical products, and the submitted studies would not be considered to be adequate provocative dermal safety evaluations of the patch product.

However, the Division recognizes the difficulty with performing 21 day sensitization/irritation studies with the active drug containing patch, particularly in products containing opioids. If the sponsor has conducted a systematic algorithm to assess and record irritation of active fentanyl containing patches in actual use conditions during the phase 3 trials, and has sufficient international post marketing experience, then the primary review division may reasonably conclude that they have an adequate safety database (b) (4). In this situation, the need for specific provocative dermal safety studies could be waived by the primary review division.

The results of these studies are not adequate to conclude that significant Contact Sensitization did or did not occur, since the open label nature of the study could incorporate observer bias. (Trial C-202-050-01)

Phototoxicity did not occur during conduct of dermal safety studies with the product, but this finding is (b) (4). (Trial C-202-053-02)

However, during the conduct of trial C-2002-050-01 an irritancy signal was noted. Therefore, if the phase 3 trial data in combination with the post marketing safety experience is deemed adequate for labeling, additional studies for topical safety may not be necessary. If the safety database is deemed not adequate, then a Cumulative Irritancy/Sensitization trial is recommended to support of the dermal safety of the sponsor's product. Additionally, DDDP recommends that Photoallergenicity study be conducted in order to complete dermal safety evaluation of the product.

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

/s/

Snezana Trajkovic
6/11/2009 01:12:29 PM
MEDICAL OFFICER

David Kettl
6/11/2009 01:34:29 PM
MEDICAL OFFICER

Susan Walker
6/15/2009 02:51:26 PM
DIRECTOR

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

Risk Assessment and Risk Mitigation Review(s)

NDA 19-813

PMR/PMC Description: Conduct an in vivo genetic toxicology study (mouse micronucleus assay) to detect chromosome aberrations with the isolated drug substance impurity (b) (4) (Impurity B).

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	October 1, 2009
Study/Clinical trial Completion Date:	January 1, 2010
Final Report Submission Date:	March 1, 2010
Other: <u>N/A</u>	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Impurity B

(b) (4)

The mouse micronucleus assay will be completed to confirm or refute the computer modeling prediction. Safety qualification is deemed acceptable to be completed post marking as the same drug substance is currently being used in the existing product. Further, the study can be completed post marketing since the December 2008 draft guidance recommending reduction of genotoxic impurities to NMT 1.5 mcg/day, represents a change in previous policy for this drug product.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A computational toxicology report that suggests a potential positive result for in vivo clastogenicity and possible carcinogenicity in the rodent.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Description: To reduce the limit of quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation at levels of no more than (NMT) (b) (4) ppm.

PMR/PMC Schedule Milestones: Final protocol Submission Date: N/A
Study/Clinical trial Completion Date: N/A
Final Report Submission Date: January 31, 2010
Other: N/A MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The Sponsor does not detect residual (b) (4) in the drug product leachable/extraction studies; however, the sensitivity of the assay methodology precludes the ability to set a specification of not more than (NMT) (b) (4) ppm, which would be equivalent to the rodent NOAEL for inhalation, induced nasal epithelial tumors. Although the proposed specification of NMT (b) (4) ppm can be met based on current methodology, the assay sensitivity should be improved in order to confirm the existing data suggesting lack of exposure. Since the assay methodology employed to date is considered adequate and appropriate based on current standards, and the (b) (4) impurity is not currently detected, this request for assay improvement can be completed post marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4) is one of the monomers employed to make the (b) (4) adhesive. Although the (b) (4) process typically removes most residual monomers, it is possible that residual monomers may remain in the final drug product. Due to the potential toxicity of residual monomers, the Sponsor was asked to measure the levels of (b) (4) via extraction studies. Although the sensitivity of the assay employed was within current expectations and no (b) (4) was detected, it is not deemed sensitive enough to confirm lower levels of (b) (4). Increasing the sensitivity of the assay will allow for more definitive confirmation of potential (b) (4). Residual monomers are below the threshold for toxicology concern of NMT 1.5 mcg/day or the NOAEL based on the existing rodent carcinogenicity. This is a PMC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is to explore means to improve the sensitivity of the analytical methodology currently employed to measure residual levels of (b) (4) in the drug product formulation. This will entail various modifications to the study conditions to determine if sensitivity can be increased.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

Depending upon the outcome of the improved analytical study, the specification for (b) (4) will be reevaluated to determine if it can be reduced to NMT (b) (4) ppm.

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Description: To reduce the limits of detection and quantitation for the analytical method for (b) (4) and perform appropriate validation to allow quantitation of this impurity at or above (b) (4) ppm. After additional collection of batch data, the specification will be reevaluated.

PMR/PMC Schedule Milestones: Final protocol Submission Date: N/A
Study/Clinical trial Completion Date: N/A
Final Report Submission Date: January 31, 2010
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The Sponsor does not detect residual (b) (4) in the drug product leachable/extraction studies; however, the sensitivity of the assay methodology precludes the ability to set a specification of less than NMT (b) (4) ppm. Although the proposed specification of NMT (b) (4) ppm can be met based on current methodology, the assay sensitivity should be improved in order to confirm the existing data suggesting lack of exposure. Since the assay methodology employed to date is considered adequate and appropriate based on current standards, and the (b) (4) impurity is not currently detected, this request for assay improvement can be completed post marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

(b) (4) is one of the monomers employed to make the (b) (4) adhesive. Although the (b) (4) process typically removes most residual monomers, it is possible that residual monomers may remain in the final drug product. Existing toxicology data suggest that (b) (4) tests positive for genotoxicity. Adequate carcinogenicity data does not exist for this potential impurity to define a NOAEL. Due to the potential toxicity of residual monomers, the Sponsor was asked to measure the levels of (b) (4) via extraction studies. Although the sensitivity of the assay employed was within current expectations and no (b) (4) was detected, it is not deemed sensitive enough to confirm lower levels of (b) (4). Increasing the sensitivity of the assay will allow for more definitive confirmation of potential (b) (4) residual monomers are below the threshold for toxicology concern of NMT 1.5 mcg/day. This is a PMC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is to explore means to improve the sensitivity of the analytical methodology currently employed to measure residual levels of (b) (4) in the drug product formulation. This will entail various modifications to the study conditions to determine if sensitivity can be increased.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
Depending upon the outcome of the improved analytical study, the specification for (b) (4) will be reevaluated to determine if it can be reduced.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Description: To evaluate the methodology for (b) (4) to determine if the sensitivity of the method can be improved to confirm that the levels of the material do not exceed 1.5 mcg/day (equivalent to (b) (4) in the product)

PMR/PMC Schedule Milestones: Final protocol Submission Date: N/A
Study/Clinical trial Completion Date: N/A
Final Report Submission Date: January 31, 2010
Other: _____ N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The Sponsor does not detect residual (b) (4) in the drug product leachable/extraction studies; The assay sensitivity should be improved in order to confirm the existing data suggesting lack of exposure. Since the assay methodology employed to date is considered adequate and appropriate based on current standards, and the (b) (4) impurity is not currently detected, this request for assay improvement can be completed post marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4) of one of the monomers employed to make the (b) (4) adhesive and is likely consumed as a monomer itself via (b) (4). Although the (b) (4) process typically removes most residual monomers, it is possible that residual monomers may remain in the final drug product. Existing toxicology data suggest that (b) (4) is limited however, it is reported to test positive in the mouse lymphoma assay for genotoxicity. Due to the potential toxicity of residual monomers, the Sponsor was asked to measure the levels of (b) (4) via extraction studies. Although the sensitivity of the assay employed was within current expectations and no (b) (4) was detected, it is not deemed sensitive enough to confirm lower levels of (b) (4). Increasing the sensitivity of the assay will allow for more definitive confirmation of potential (b) (4) residual monomers are below the threshold for toxicology concern of NMT 1.5 mcg/day. This is a PMC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is to explore means to improve the sensitivity of the analytical methodology currently employed to measure residual levels of (b) (4) in the drug product formulation. This will entail various modifications to the study conditions to determine if sensitivity can be increased.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
Depending upon the outcome of the improved analytical study, a specification for (b) (4) may be required, particularly if the assay suggests that levels would exceed the threshold of toxicological concern.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
 - ☐ Assess a known serious risk related to the use of the drug?
 - ☐ Assess signals of serious risk related to the use of the drug?
 - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The report to be prepared by the Sponsor will include greater detail regarding how they established the specificity of the assays employed to identify the potential leachables/extractables.

Required

- ☐ Observational pharmacoepidemiologic study
 - ☐ Registry studies
- Continuation of Question 4
- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Description: To conduct the Probe Tack test and submit the test method, validation report and specification.

PMR/PMC Schedule Milestones: Final protocol Submission Date: N/A
 Study/Clinical trial Completion Date: N/A
 Final Report Submission Date: December 31, 2009
 Other: _____ N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The Probe Tack test is intended to obtain precise measurements of adhesion, tack, quick stick and cohesion of transdermal patches. These attributes are critical to ensure that the patch remains in place and does not fall off over the period of use (72 hrs). Although there are currently clinical data via the use of this product overseas, and the current patch is also labeled for potential overlay to avoid loss of the patch and accidental exposures, these measurements will be used to refine the patch characteristics and improve overall product quality.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Probe Tack testing is currently considered state of the art for transdermal patch development and is being incorporated into all newer development programs. The goals of these studies will provide a more quantitative measurement of patch adhesion.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
 - ☐ Assess a known serious risk related to the use of the drug?
 - ☐ Assess signals of serious risk related to the use of the drug?
 - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
 - ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
 - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
 - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Probe Tack testing methodology employ standardized methodology.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19813	SUPPL 44	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	DURAGESIC

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/s/

KATHLEEN M DAVIES
07/30/2009

LARISSA LAPTEVA
07/30/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-813/S044

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



PDUFA GOAL DATE EXTENSION

NDA 19-813/S-044

Ortho-McNeil-Janssen Pharmaceuticals, Inc
(c/o) Johnson & Johnson Pharmaceutical Research and Development, LLC
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Attention: Harindra Abeysinghe, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abeysinghe:

Please refer to your January 30, 2009 supplemental new drug application, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic[®] (fentanyl transdermal system) 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h.

On May 21, 2009, we received your May 19, 2009 major amendment to this application. The receipt date is within two months of the user fee goal date. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is July 30, 3009.

If you have any questions, call Kathleen Davies, Regulatory Health Project Manager, at 301-796-2205.

Sincerely,

{See appended electronic signature page}

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

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/s/

Matthew Sullivan
5/28/2009 12:12:03 PM
For Sara Stradley, M.S.

May 19, 2009

Swati Patwardhan, MS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of Post-Marketing Evaluation
Phone (301) 796-4085
Fax (301) 796-9748

Reference: **Drug Master File No.** (b) (4)
Title of Submission: (b) (4)
Holder of Submission: (b) (4)

Dear Ms. Patwardhan,

(b) (4) does not have any objection for FDA discussing the above reference product with Johnson & Johnson regarding their NDA supplement 19-813.

Please give me if you need any additional information.

Sincerely yours,

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/s/

Kathleen Davies
7/21/2009 12:16:35 PM
CSO
Faxed to FDA due to action date approaching.



METHODS VALIDATION MATERIALS RECEIVED

NDA 19-813/SCF-044

Harindra Abeysinghe, Director, Regulatory Affairs
Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Dr. Harindra Abeysinghe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (Fentanyl Transdermal System) Patch and to our April 22, 2009 letter requesting sample materials for methods validation testing.

We acknowledge receipt on April 30, 2009 of the 18 sample holders and (b) (4) that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have any questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@ fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
4/30/2009 01:59:15 PM



REQUEST FOR METHODS VALIDATION MATERIALS

NDA 19-813

Harindra Abeysinghe, Director, Regulatory Affairs
Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Dr. Harindra Abeysinghe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (Fentanyl Transdermal System) Patch.

We will be performing methods validation studies on Duragesic (Fentanyl Transdermal System) Patch as described in NDA 19-813.

In order to perform the necessary testing, we request the following sample materials and equipments in addition to the materials received April 13, 2009:

<u>Materials</u>	<u>Quantity</u>
USP <724>Apparatus 7 sample holders	7
(b) (4)	1

These items will be returned after the method validation studies are completed.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader

Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
4/22/2009 03:34:47 PM



METHODS VALIDATION MATERIALS RECEIVED

NDA 19-813/SCF-044

Harindra Abeysinghe, Director, Regulatory Affairs
Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Dr. Harindra Abeysinghe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (Fentanyl Transdermal System) Patch and to our March 27, 2009 letter requesting sample materials for methods validation testing.

We acknowledge receipt on April 13, 2009 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have any questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
4/15/2009 06:31:18 PM



REQUEST FOR METHODS VALIDATION MATERIALS

NDA 19-813

Harindra Abeysinghe, Director, Regulatory Affairs
Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
Titusville, new Jersey 08560-0200

Dear Dr. Harindra Abeysinghe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (Fentanyl Transdermal System) Patch.

We will be performing methods validation studies on Duragesic (Fentanyl Transdermal System) Patch as described in NDA 19-813.

In order to perform the necessary testing, we request the following sample materials and equipments:

Methods

The current methods for the Peel Force, Tack and Release Rate

Sample

4 times the number of Duragesic (Fentanyl Transdermal System) Patch required to perform the Peel Force, Tack and Release Rate tests.

Materials

If the Peel test uses a substrate other than stainless steel send 4 times the amount required to perform the Peel test.

Any non-standard or specialized materials specified in the Peel Force, Tack or Release Rate methods. Send enough material to allow the tests to be performed 4 times.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James Allgire
1114 Market Street, Room 1002

St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire
3/27/2009 05:06:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST

TO: FDA
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Swati Patwardhan, RPM,
E-mail Address: swati.patwardhan@fda.hhs.gov
Phone: (301)-796-4085
Fax.: (301)-796-9748

Through: Eric Duffy-Division Director, Post marketing Division (Ph: 301-796-1666)
Ramesh Raghavachari, Pharmaceutical Assessment Lead, (Ph: 301-796-1738)

and

Michael Folkendt, ONDC Methods Validation Coordinator, HFD-800
Phone: 301-796-1670

SUBJECT: Methods Validation Request

Application Number: NDA 19-813/SCF-044

Name of Product: Duragesic® (fentanyl Transdermal System) Patch

Applicant: **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**

Applicant's Contact Person: Harindra Abeysinghe, Director, Regulatory Affairs

Address: 1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Telephone: (609) 730-6212 Fax: 609-730-3091

Date NDA(supplement) Received by CDER: **January 30, 2009**

Chemical/Therapeutic Type:

Date of Amendment(s) containing the MVP: **requested**

Special Handling Required: No

DATE of Request: **March 26, 2009**

DEA Class: N/A

Requested Completion Date: **May 15, 2009**
Package

Format of Methods Validation

PDUFA User Fee Goal Date: **May 30, 2009**

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report*

Summary, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 19-813
← SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
↑ Contents of Attached Methods Validation Package:				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				
Specifications/Methods for New Drug Substance(s)				
Specifications/Methods for Finished Dosage Form(s)				
Supporting Data for Accuracy, Specificity, etc.				
Applicant's Test Results on NDS and Dosage Forms				
Other:				
→ REQUESTED DETERMINATIONS (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)				
Method ID	Method Title	Volume/Page	MV Request Category (see attached page)	Comments
	Peel force		2	
	Tack		2	
	Release Rate		2	
Additional Comments: The supplement provides for new formulation for trans-dermal delivery of fentanyl. The supplement is located in EDR: \CDSESUB1\EVSPROD\NDA019813\0017. However, the method is not provided in the original submission. We have requested the methods to be submitted to the NDA-supplement. So that we don't further delay this request, we are sending this consult now and ask that you include a request for a copy of the Methods and Method Validation package from the applicant when you request the samples and materials. The applicant can reference the date of electronic submission if they submit it to NDA supplement prior to responding to your request.				

Methods Validation Request Criteria

MVP Request Category	Description
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason.

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/s/

Michael Folkendt
3/27/2009 03:10:28 PM



NDA 19-813/S-044

PRIOR APPROVAL SUPPLEMENT

Ortho-McNeil-Janssen Pharmaceuticals, Inc.
(c/o) Johnson & Johnson Pharmaceutical Research and Development, LLC
1000 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Attention: Harindra Abeysinghe, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abeysinghe:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: DURAGESIC[®] (fentanyl transdermal system)

NDA Number: 19-813

Supplement number: 044

Date of supplement: January 30, 2009

Date of receipt: January 30, 2009

This supplemental application proposes the following changes: revised formulation for the transdermal delivery of fentanyl.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 30, 2009.

We also acknowledge your request for expedited review of this application. We are granting this expedited review.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Anesthesia, Analgesia
and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kathleen Davies
2/26/2009 10:04:51 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Division of Dermatology and Dental Products (HFD-540)			FROM (Name, Office/Division, and Phone Number of Requestor): Kathleen Davies, RPM, Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)	
DATE April 15, 2009	IND NO.	NDA NO. 19813	TYPE OF DOCUMENT Prior Approval Supplement	DATE OF DOCUMENT January 30, 2009
NAME OF DRUG Duragesic (fentanyl transdermal product)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Opioid	DESIRED COMPLETION DATE May 15, 2009
NAME OF FIRM: Johnson and Johnson				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☐ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES ☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS				
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL ☐ NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: DAARP has a CMC prior approval supplement for Duragesic, NDA 19-813. This is a conversion from a reservoir patch to a matrix patch. DAARP requests Derm evaluate two studies in the CMC submission related to contact sensitization and photosensitivity. This product, D-Trans, which they used in these studies is the same as the proposed matrix Duragesic product proposed. The reports are located in Module 5.3.5.4, and are the study reports for protocols 2-2002-050 and c-2002-053. Link to EDR: \\CDSESUB1\EVSPROD\NDA022348\022348.ENX PDUFA: May 30, 2009 (however, we may extend the clock 2 months under a major amendment). MO: Elizabeth Kilgore PM: Kathleen Davies				
SIGNATURE OF REQUESTOR Kathleen Davies, Regulatory Health Project Manager			METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

Kathleen Davies
4/15/2009 01:56:51 PM