

**ABSOLUTE BIOAVAILABILITY/PHARMACOKINETIC AND RESIDUAL DRUG  
ANALYSIS OF DURAGESIC® TRANSDERMAL SYSTEM AND GENERIC  
FENTANYL TRANSDERMAL SYSTEM IN HEALTHY ADULTS**

**Short title:** Fentanyl Patch Pharmacokinetics in Healthy Adults

**U01 Principal Investigator:**

Audra L. Stinchcomb (contact), PhD, RPh

**Medically Accountable Investigator:**

Jeffrey Fink, MD, MS

**Sponsor:**

Food and Drug Administration

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## **STATEMENT OF COMPLIANCE**

This study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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## PROTOCOL SUMMARY

**Title:** Absolute Bioavailability/Pharmacokinetic and Residual Drug Analysis of Duragesic® Transdermal System and Generic Fentanyl Transdermal System in Healthy Adults

**Population:** Healthy, non-smoking adults age 18-45 years

**Number of Sites:** Single site: University of Maryland School of Medicine/General Clinical Research Center (GCRC)

**Study Duration:** Approximately up to 18 months

**Subject Participation Duration:** Approximately 12-18 weeks including the screening Session

**Description of Study Products:** Fentanyl citrate injection, Fentanyl Duragesic®, matrix type, Janssen Pharmaceuticals transdermal drug delivery system (TDDS); Mylan (fentanyl) matrix type, Mylan Pharmaceuticals TDDS; naltrexone hydrochloride oral tablets and naloxone hydrochloride injections

**Objective:** To determine serum fentanyl levels after using reference (Duragesic®) and generic fentanyl (Mylan) TDDS, and comparing them to the serum levels of intravenous fentanyl citrate, in healthy adult subjects

**Description of Study Design:** This will be a three treatment, open-label, randomized, crossover clinical study with a Run-In Study Session (Study Session I) of intravenous fentanyl citrate, followed by a transdermal administration of a single strength of the reference listed drug (RLD) Duragesic®, and a transdermal administration of a generic equivalent to the RLD, Mylan fentanyl TDDS. A total of 24 subjects will be enrolled to complete this study.

*A) Pharmacokinetic Determination of Strength*

The study will be a three treatment, open-label, randomized crossover study, with a Run-In Study

Session I of an intravenous fentanyl citrate administration, with at least a one week washout interval between Study Sessions.

The study products are:

- Single intravenous (100 µg) administration of fentanyl citrate (50 µg/mL)
- Duragesic® TDDS containing fentanyl (25 µg/h) to be worn for 3 days (72h)
- Mylan fentanyl TDDS (Generic) containing fentanyl (25 µg/h) to be worn for 3 days (72h)

Each Subject will be his/her own control.

Administration of naloxone injection will be used to test for withdrawal prior to using any study products, and to be used emergently in case of fentanyl toxicity. Naltrexone oral tablets will be used to block the opioid receptors to avoid any clinical effects or side-effects of fentanyl.

Blood samples will be obtained as follows (based on administration route):

- 60 min pre-IV administration and then up to 36 hr (1.5 days) post start of IV administration
- 60 min pre-application and then up to 192 hr (8 days), during 3 day wear and post removal of RLD
- 60 min pre-application and then up to 192 hr (8 days), during 3 day wear and post removal of Generic product

*B) Residual Drug Analysis determination of Strength*

In conjunction with the above described study residual drug analysis will also be conducted for the used RLD and Generic TDDS described in Part A.

- Prior to administration to the Subject as described in Part A, the TDDS will be weighed and the weight recorded.
- The pouch, release liner and all items coming into contact with the TDDS (gloves, forceps, etc.) to be applied in Part A will be retained for analysis.
- The used TDDS will be retained for drug content analysis.
- Upon removal of the product after prescribed wear Session, the skin (at site of application) will be swabbed and the swab retained for drug content analysis.
- All items coming into contact with the TDDS during removal from the Subject and storage in a separate labeled sealable foil pouch for analytical retention will be analyzed for drug content.

## 1 KEY ROLES

**U01 Principal Investigator:** Audra L. Stinchcomb (contact), PhD, RPh  
Professor, Department of Pharmaceutical Sciences  
University of Maryland School of Pharmacy  
20 N Pine St, Room PHN521  
Baltimore, MD 21201  
Phone: 410-706-2646  
Fax: 410-706-0886  
Email: [astinchc@rx.umaryland.edu](mailto:astinchc@rx.umaryland.edu)

**Medically Accountable  
(Clinical) Investigator:** Jeffrey C Fink M.D., M.S.  
Professor  
Department of Medicine  
Department of Epidemiology and Public Health  
University of Maryland School of Medicine  
UMMC, Room NN3E03  
Baltimore, MD 21201  
Phone: 410-328-4822  
Fax: 410-328-5685  
E-mail: [jfink@medicine.umaryland.edu](mailto:jfink@medicine.umaryland.edu)

## 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

### 2.1 Background Information

There are numerous transdermal drug delivery systems (TDDS) that are currently available in the United States, the first of which was approved by the Food and Drug Administration (FDA) in 1979 [1]. Transdermal drug delivery systems (TDDS) available in the form of patches are convenient, attractive, and easy to use systems. Fentanyl is a very popular TDDS available on the United States market today. Drug release from these TDDS varies significantly and is dependent on a number of factors including system design, physicochemical properties of the drug, excipients, occlusion, sweat, skin condition, skin type and temperature. Investigating the influence of these factors on drug release from reference and generic products that are often available in different forms is important to ensure that generic products are not less safe than the reference product. Accurate determination of the rate and extent of drug release and absorption is crucial to ensure the safety of individuals using this and other types of TDDS.

Positive outcome of this project will identify appropriate methods to determine the rate and extent of drug release and absorption from TDDS, and will help regulatory agencies in the development of Guidances for Industry regarding the characterization of drug release and absorption kinetics to ensure the safety of individuals utilizing these types of products.

### 2.2 Rationale

The rationale of this study is to determine the delivery rate and the extent of absorption of fentanyl drug release from FDA-approved TDDS products (reference e.g. Duragesic®, versus Mylan transdermal patches) that have different inactive ingredients. can be determined in humans by accurately quantifying residual drug from TDDS post-wear, and the delivery rate can be determined in pharmacokinetic studies. This study will compare fentanyl levels by using in vitro skin flux permeation studies, as a predictor of in-vivo bioequivalence and pharmacokinetics of Duragesic® and Mylan fentanyl TDDS. This will be done through development of an appropriately controlled and well-characterized in-vitro methodology to quantify the in-vivo exposure of healthy adults to fentanyl during TDDS wear, so that the rate of drug delivery can be defined in a manner that can help the regulatory agency (FDA) in developing Guidance for Industry regarding the characterization of drug release and absorption kinetics to ensure the safety of individuals utilizing these types of products.

In the clinical study component, we will employ two types of evaluation to determine the rate and extent of drug release and absorption from fentanyl TDDS, namely residual drug analysis post-wear and pharmacokinetic analysis in healthy adult Subjects. In addition, we will compare the serum drug concentrations following TDDS and intravenous administration, in

order to explore bioequivalence of these TDDSs. We will conduct residual drug analysis of TDDS following in vivo wear using highly sensitive validated quantification methods.

**Duragesic® versus Mylan (fentanyl) TDDS**

	<b>Duragesic®</b>	<b>Mylan (fentanyl) TDDS</b>
Inactive ingredients	polyester/ethyl vinyl acetate, polyacrylate adhesive	dimethicone NF, polyolefin film backing, silicone adhesive
TDDS type	Matrix	Matrix
Manufacturer	Janssen	Mylan



### 3 OBJECTIVES

#### 3.1 Study Objectives

The objectives of this open label, randomized, crossover study are to

- To explore bioequivalence of Duragesic® transdermal system and generic Mylan fentanyl TDDS, and compare bioavailability to direct IV infusion of fentanyl citrate.
- To conduct release rate analysis of generic fentanyl (Mylan) TDDS compared to Duragesic® TDDS.
- To determine the residual drug content of the Duragesic® and generic fentanyl TDDS.

#### 3.2 Study Outcome Measures

The main outcome measure of the study is the determination of the pharmacokinetic parameters of fentanyl in healthy adult Subjects (i.e., clearance (CL), volume of distribution (V), elimination rate constant ( $K_{el}$ ), maximum serum concentration ( $C_{max}$ ); time of maximum serum concentration ( $T_{max}$ ) of fentanyl and area under the serum concentration-time curve (AUC). In addition, we will determine residual drug content from worn Duragesic® and Mylan fentanyl TDDS to estimate total amount of absorbed fentanyl from each.

## 4 STUDY DESIGN

This is a three treatment open-label, randomized cross-over clinical study with a Run-In Study Session I of intravenous fentanyl citrate, followed by randomization to Duragesic® and generic fentanyl in a sequential, 2-Session fashion with at least a one week wash-out Session between the sessions.

The study design is shown below:

Study Session I (Run-in)	Randomization		Study Session II	Study Session III
Intravenous -Fentanyl		Study Arm 1	Duragesic®	Mylan Fentanyl
		Study Arm 2	Mylan Fentanyl	Duragesic®

The study will consist of a total of twenty-five Study Days (24 Subjects) within three Study Sessions, with at least a one week washout Session between successive Study Sessions. The half-life of fentanyl is approximately 24 hours. Hence, 5 days (i.e. 5 half-lives) will be sufficient for >95% of fentanyl to be eliminated from the body. Each of the 24 Subjects will be enrolled to complete all twenty-five study days (Run-In Study Session I = 5 Study Days; Study Sessions II and III = 10 Study Days each). The study is open label and not blinded, because PK assessment is not subject to participant and/or observer bias. After each Study Session is completed, the available safety data will be reviewed by an Independent Safety Monitor (ISM) to determine whether or not to proceed to the next Study Session.

Considering the objective of the study to explore bioequivalence of Duragesic® and generic fentanyl and to conduct release rate analysis of generic fentanyl to Duragesic®, the above study design would adequately address both questions. The randomization to sequences [Reference (R) –Test (T), T-R] would appropriately take into account the sequence and the Session effect for bioequivalence evaluations. Having all Subjects enter the intravenous Run-In Study Session I initially would also help in accurate determination of absolute bioavailability for Duragesic® and generic Mylan fentanyl in this study.

Each Subject will be his/her own control and each Subject will sign an institutional review board–approved consent form explaining the purpose, nature, risks, benefits, and duration of the study. The study will be conducted in accordance with good clinical practice guidelines and with the ethical principles originating in the Declaration of Helsinki.

**The three Study Sessions are as follows:**

**Study Session I (Run-in):**

Each of the 24 Subjects will start the study with the Run-In Session of intravenous fentanyl citrate infusion by giving a single-dose of 100 µg fentanyl citrate infusion (2 mL over 2 minutes) as described in the Manual of Procedures. Each Subject will receive a naltrexone hydrochloride 50 mg oral tablet 12-17 hours  $\pm$  1 hour before and again shortly prior to intravenous administration and then as described below after intravenous administration for 7 additional doses, for a total of nine 50 mg oral doses of naltrexone hydrochloride tablets.

**Study Session II:**

Twelve Subjects will be randomized to Study Arm 1 which will receive the Duragesic® fentanyl TDDS (25 µg/h); and other 12 Subjects to Study Arm 2 which will receive the Mylan fentanyl TDDS (25 µg/h). The patches will be applied for 3 days on each Subject. The Subject's skin in the area of application (upper arm region) will be relatively free of hair before TDDS application. Each Subject will receive a naltrexone hydrochloride 50 mg oral tablet 12-17 hours  $\pm$  1 hour before and again shortly prior to patch application and then as described below after patch application for 16 additional doses, for a total of eighteen 50 mg oral doses of naltrexone hydrochloride tablets.

**Study Session III:**

The 12 Subjects who were randomized to Study Arm 1 to receive the Duragesic® fentanyl TDDS (25 µg/h) will cross-over to receive the Mylan fentanyl TDDS (25 µg/h) applied; and the other 12 Subjects who were randomized to Study Arm 2 to receive the Mylan fentanyl TDDS (25 µg/h) will now cross-over to receive the Duragesic® fentanyl TDDS (25 µg/h). The patches will be applied for 3 days on each Subject. Each Subject will receive a naltrexone hydrochloride 50 mg oral tablet 12-17 hours  $\pm$  1 hour before and again shortly prior to patch application and then as described below after patch application for 16 additional doses, for a total of eighteen 50 mg oral doses of naltrexone tablets.

## 5 STUDY ENROLLMENT AND WITHDRAWAL

Only adult Subjects who meet the inclusion/exclusion criteria will be eligible for enrollment into this study. Twenty-four Subjects will be recruited and at least 10 alternates will be screened, as needed, to ensure that any dropouts will be replaced until a total of 24 Subjects complete all study procedures. The study population selected for this study includes healthy non-smoking adult men and women ages 18 to 45, inclusive. The selection criteria are designed to exclude persons who might have medical conditions that could pose a safety risk and persons whose medical conditions might interfere with the objectives and results of the study.

### 5.1 Subject Inclusion Criteria

Subjects are eligible for this study if they fulfill the inclusion criteria specified below:

1. Men or non-pregnant women of any ethnic background between the age of 18 and 45 years old.
2. Subjects must be non-smokers (must have refrained from the use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes) over the previous 2 months and are not currently using tobacco products.
3. Provide written informed consent before initiation of any study procedures.
4. Available for follow-up for the planned duration of the study.
5. Able to communicate well with the investigators.
6. Able to adhere to the study protocol schedule, study restrictions and examination schedule.
7. Subjects who are within their ideal body weight (BMI between  $>17$  and  $\leq 28$  Kg/m<sup>2</sup>).
8. Subjects deemed to be healthy as judged by the Medically Accountable Investigator (MAI) and determined by medical history, physical examination, and medication history.
9. Subjects have no history of the following: ongoing acute or intermittent pain, postoperative pain, respiratory compromise, acute or severe asthma, or constipation (less than 1 bowel movement every 2 days).
10. Negative urine drug screening test at time of screening.
11. Have normal screening laboratories for WBC, Hgb, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT, AST and bilirubin.
12. Have normal screening laboratories for urine protein and urine glucose.
13. Female Subjects must be of non-childbearing potential (as defined as surgically sterile [i.e. history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year[no bleeding for

- 12 consecutive months), or if of childbearing potential must be non-pregnant at the time of enrollment and on the morning of the first day of each Study Session, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner.
14. Agrees not to participate in another clinical study or to participate in an investigational drug study for at least 1 month after last Study Session.
  15. Agrees not to donate blood to a blood bank throughout participation in the study and for at least 3 months after last Study Day.
  16. Have a normal ECG; must not have the following to be acceptable: pathologic Q wave abnormalities, significant ST-T wave changes, left ventricular hypertrophy, right bundle branch block, left bundle branch block. (sinus rhythm is between 55–100 beats per minute).
  17. Have normal vital signs:
    - Temperature 35-37.9°C (95-100.3°F)
    - Systolic blood pressure 90-140 mmHg
    - Diastolic blood pressure 60-90 mmHg
    - Heart rate 55-100 beats per minute
    - Respiration rate 12-18 breaths per minute

## 5.2 Subject Exclusion Criteria

Subjects will be excluded for any of the following conditions/reasons:

1. Women who are pregnant, lactating or breast feeding or have a positive serum pregnancy test at enrollment or positive urine pregnancy test on the morning of the first day of any Study Session.
2. Smokers (current use or use over the previous 2 months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes).
3. Participation in any ongoing investigational drug trial or clinical drug trial.
4. History of chronic obstructive pulmonary disease or cor pulmonale, or substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression.
5. Active positive Hepatitis B, C, and HIV serologies.
6. Positive urine drug screening test.
7. Use of any prescription medication during the Session 0 to 30 days or over-the counter medication e.g. antihistamines or topical corticosteroids (vitamin, herbal supplements and birth control medications not included) during the Session 0 to 3 days before entry to the study.
8. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product or agents deemed to be immunosuppressive as determined by physician investigator within 72 hours prior to dosing (e.g. antihistamines, systemic or topical corticosteroids (within 3 weeks prior to dosing), cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).

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9. Use of monoamine oxidase inhibitors 21 days prior to study.
  10. Current use of mixed agonist/antagonist (such as pentazocine, nalbuphine or butorphanol) and partial agonist (buprenorphine) analgesics.
  11. Current use of anticholinergics or other medications with anticholinergic activity.
  12. Consumption of beverages containing alcohol, grapefruit juice, Seville oranges, or quinine (e.g. tonic water) or foods containing poppy seeds in the last 72 hours.
  13. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
  14. Any prior serious adverse reaction or hypersensitivity to fentanyl, morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, naltrexone or naloxone or any of the inactive ingredients in the TDDS (polyester/ethyl vinyl acetate, polyacrylate adhesive, silicone adhesive, dimethicone NF, or polyolefin).
  15. Have a diagnosis of schizophrenia or other major psychiatric diagnosis or mental illness (e.g., major depression).
  16. Medical history of personal drug or alcohol addiction or abuse).
  17. Any condition that would, in the opinion of the Medically Accountable Investigator (MAI), place the Subject at an unacceptable risk of injury or render the Subject unable to meet the requirements of the protocol.
  18. Inability to communicate or co-operate with the investigators.
  19. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application site (upper arm), sunburn, raised moles and scars, open sores at application site (upper arm), scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
  20. Failure to pass opioid dependence challenge test on the first Study Day of any Study Session (i.e., before taking the first dose of naltrexone hydrochloride). Each Subject will be injected subcutaneously with naloxone hydrochloride (0.8 mg injection) and will be observed for 45 minutes for signs and symptoms of opioid withdrawal.
  21. Within 4 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product or agents deemed to be immunosuppressive as determined by physician investigator.

## 6 STUDY PRODUCT

### 6.1 Study Product Description

#### 6.1.1 Duragesic® (fentanyl) TDDS 25 µg/h

Duragesic® is a prescription TDDS that contains fentanyl which is a federally controlled substance (CII). Duragesic® TDDSs deliver fentanyl at a rate of 25 µg/h and are only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

#### 6.1.2 Mylan (fentanyl) TDDS 25 µg/h

Mylan (fentanyl) is a prescription TDDS that contains fentanyl which is a federally controlled substance (CII). Mylan (fentanyl) TDDS deliver fentanyl at a rate of 25 µg/h and are only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

#### 6.1.3 Fentanyl citrate injection, USP 0.05 mg/mL

Fentanyl citrate injection is a prescription that contains fentanyl which is a federally controlled substance (CII). Fentanyl citrate (100 µL, 2 mL) will be administered with a syringe over 2 min through the catheter into the vein. Fentanyl citrate is for patients for short duration analgesic action during anesthetic Sessions (premedication, induction, maintenance, and immediate postoperative), analgesic supplement with anesthesia, administration of anesthetic agent with oxygen in selected high risk patients.

#### 6.1.4 Naltrexone hydrochloride tablets, USP 50 mg

Naltrexone hydrochloride is an opioid antagonist which attenuates or reversibly blocks the effects of opioids. It is available as a prescription medication and is used to treat opioid addiction and alcoholism.

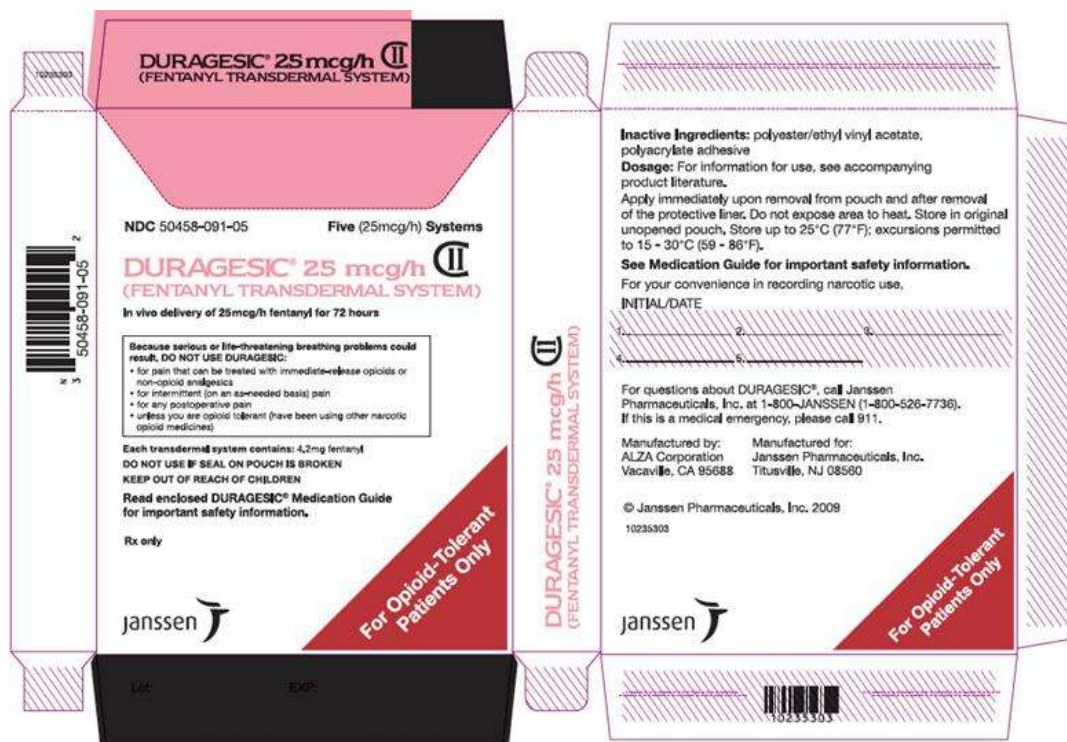
#### 6.1.5 Naloxone hydrochloride injection, USP 0.4 mg/mL

Naloxone hydrochloride is an opioid antagonist which attenuates or reversibly blocks the effects of opioids. It is available as a prescription medication and is used for the complete or partial reversal of opioid respiratory and/or central nervous system depression.

## 6.2 Formulation, Packaging, and Labeling

### 6.2.1 Duragesic® (fentanyl) TDDS 25 µg/h

Active ingredient (in each TDDS): Fentanyl, 25 µg delivered per hour. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the TDDS: polyester/ethyl vinyl acetate and a polyacrylate adhesive. This is a matrix type TDDS, manufactured by ALZA Corporation and distributed by Janssen Pharmaceuticals, Inc. This product should be stored below 25°C (77°F). Excursions permitted at 15-30°C.



### 6.2.2 Mylan (fentanyl) TDDS 25 µg/h

Active ingredient (in each TDDS): Fentanyl, 25 µg delivered per hour. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the TDDS: dimethicone NF and silicone adhesive and polyolefin film backing. This is a matrix type TDDS, manufactured by Mylan Pharmaceuticals Inc. This product should be stored between 20°-25°C (68°-77°F).





### 6.2.3 Fentanyl citrate, preservative free, injection 0.05 mg/mL

Active ingredient: Fentanyl, each mL contains fentanyl citrate equivalent to 50 µg (0.05 mg) fentanyl base. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the injectable: water for injection, pH 4.0-7.5: sodium hydroxide and/or hydrochloric acid, if needed, for pH adjustment. This injectable is manufactured by West-Ward Pharmaceuticals. This product should be stored between 20°-25°C (68°-77°F).



#### 6.2.4 Naltrexone hydrochloride tablets, USP 50 mg

Active ingredient (in each tablet): Naltrexone hydrochloride, USP 50 mg. In addition to the active ingredient (naltrexone hydrochloride), the following inactive ingredients are present in the tablet: crospovidone, hypromelloses, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycols, polysorbate 80, silicon dioxide, titanium dioxide, ferric oxide yellow and ferric oxide red. This oral tablet manufactured by Covidien Ltd., or a comparable generic equivalent, will be procured by the investigational drug pharmacy at the University of Maryland Medical Center from the appropriate distributor (e.g. Mallinckrodt Pharmaceuticals). This product will be stored at room temperature, 20 to 25°C (68 to 77°F).



#### 6.2.5 Naloxone hydrochloride injection, USP 0.4 mg/mL

Active ingredient (in each injection): Naloxone hydrochloride, USP 0.4 mg/mL is a sterile, nonpyrogenic solution of naloxone hydrochloride in water for injection from Hospira (Lake Forest, Illinois), or a comparable generic equivalent, will be procured by the investigational drug pharmacy at the University of Maryland Medical Center from the appropriate distributor. Each mL contains naloxone hydrochloride and sodium chloride to adjust tonicity in water for injection. May contain hydrochloric acid for pH adjustment; pH 4.0 (3.0 to 6.5). The single dose ampoule is for intravenous, intramuscular or subcutaneous use. This product will be stored at room temperature, 20 to 25°C (68 to 77°F).



## 8 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

### 8.1 Study Hypotheses

Given the fact that there are formulation differences between Duragesic® and Mylan fentanyl TDDS, we hypothesize that:

- a. Bioequivalence exploration.
- b. Release rate analysis.

These hypotheses will be tested by comparing the residual drug amounts in Duragesic® and Mylan fentanyl TDDS and by assessing the pharmacokinetic parameters following their application, and comparing them to the pharmacokinetic parameters estimated after direct IV infusion of fentanyl citrate.

### 8.2 Pharmacokinetics (PK) Analyses

#### 8.2.1 Pharmacokinetic endpoints

- Area under the time curve from dosing time to last measurement time ( $AUC_{0-t}$ ) and peak drug activity ( $C_{max}$ ) for Duragesic® TDDS and Mylan fentanyl TDDS will be used as the primary endpoint. For intravenous fentanyl,  $AUC_{0-\infty}$  will be determined.
- The time to maximum concentrations ( $T_{max}$ ) and  $AUC_{0-\infty}$  for fentanyl from Duragesic® TDDS and Mylan fentanyl TDDS will also be determined.

### 8.3 Final Analysis Plan

The primary statistical analysis will be performed on the natural log transformed  $AUC_{0-t}$ ,  $AUC_{0-A}$  and  $C_{max}$  of Fentanyl from the three Study Sessions using SAS V 9.3. A linear mixed effects model will be used to assess the effects of treatment, Session, sequence and Subject within sequence on natural log transformed  $AUC_{0-t}$ ,  $AUC_{0-C}$  and  $C_{max}$ . The treatment, Session, sequence effect will be treated as fixed effects and assessed at a significance level of 0.05. The Subject within sequence will be treated as a random effect. Intra and inter individual variabilities will be obtained. The least square mean estimates for the adjusted differences between treatment means (the log transformed  $AUC_{0-t}$ ,  $AUC_{0-C}$  and  $C_{max}$ ) and the standard error associated with these differences will be obtained. The geometric means for  $AUC_{0-a}$  will be obtained by exponentiating the log transformed  $AUC_{0-i}$  for all the three treatments to determine the absolute bioavailability.

The absolute bioavailability for Duragesic® TDDS and Mylan fentanyl TDDS will be calculated.

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*The analyses for IV administration of fentanyl citrate will be as follows:*

Non compartmental and compartmental analyses will be conducted to estimate the PK parameters such as clearance, volume of distribution, elimination rate constant, maximum serum concentration; time of maximum serum concentration and area under the serum concentration-time curve. All analyses will be conducted using Phoenix® WinNonlin® 6.3 (Pharsight, a Certara Company, CA). Absolute bioavailability will be calculated.

*The analyses for both TDDS applications (Duragesic® and Mylan fentanyl) will be as follows:*

The serum fentanyl concentrations will be determined and the PK parameters such as  $C_{max}$ ,  $T_{max}$ , AUC, steady concentrations ( $C_{ss}$ ) of fentanyl in each Subject will be elucidated. The rate of fentanyl absorption in each Subject is calculated by dividing the  $C_{ss}$  by the clearance predicted from the IV bolus data.

Cumulative amount of fentanyl released by Duragesic® at the end of study Session will be obtained by subtracting residual fentanyl still remaining in the TDDS at the end of the study Session from the total amount of the drug present in an unused TDDS.

Similarly, cumulative amount of the drug released by the Mylan TDDS at the end of study Session is computed.

The rate of drug release from Duragesic® and Mylan TDDS will be determined.

The means of fentanyl release rates from Duragesic® TDDS, standard deviations from their mean, and 95% confidence intervals will be determined and tabulated. The statistical significance of difference between the means will be evaluated by two-tailed Student's t-test.